

Month of Birth and Risk of Immediate Hypersensitivity to Seasonal and Nonseasonal Antigens

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ABSTRACT

The risk of immediate hypersensitivity to seasonal allergens has been reported to vary with month of birth. Serum samples from 631 children less than 18 years of age from the Detroit area were measured for allergen-specific immunoglobulin E (IgE) using an enzyme-linked immunosorbent assay. IgE to the seasonal allergens ragweed, timothy, and mite were measured, as well as to the relatively nonseasonal allergens cat, dog, and *Alternaria*. The number of positive tests for IgE ranged from 32% for mite to 58% for cat. The birth month distribution of children with positive tests was compared to the birth month distribution of all births in the Detroit metropolitan area. Some patterns were consistent with previous studies; however, there were no statistically significant differences with respect to the comparison population. Children with positive results to ragweed tended to be born more often during the August–October ragweed season. Sensitivity to mite was most common in July and August, a time period associated with high humidity in metropolitan Detroit. Children positive for cat IgE were more often born in February, July, and November; subjects positive to dog during June–September and children positive to *Alternaria* peaked in July. In contrast to other studies, children with positive IgE to timothy tended to be born less often during the May–June grass season.

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INTRODUCTION

ALLERGIC DISEASE is a major childhood health problem affecting an estimated 10–20% of the U.S. pediatric population.⁽¹⁾ Researchers have hypothesized that relatively high exposure to allergens during a critical period in the first months of life may predispose to the development of atopic disease. Multiple studies examining the birth month distributions of populations of allergic children and adults from Scandinavia, Italy, England, Australia, and the United States have yielded conflicting results. In many studies a significant association was reported between birth just prior to or during a pollen season and an increased frequency of sensitization to the pollen. The purpose of this study was to evaluate the association of total and allergen-specific immunoglobulin E (IgE) concentration levels among children 18 years and younger with birth month distribution.

METHODS

From 1979 to 1985, the Henry Ford Hospital Pediatric Allergy Research Laboratory tested 442 consecutive serum specimens from Detroit area children under 19 years of age who were clinically suspected of having allergic disease. Sera from an additional 189 children tested for another study,⁽²⁾ 91 with clinical allergy and 98 without, were included to bring the total number of subjects to 631.

Collected serum was separated as soon as possible and stored at -20°C until assayed. Total IgE and allergen-specific IgE levels were quantitated as previously described using an enzyme-linked immunoassay.⁽³⁾ For total IgE determination, 12-well polystyrene micro-titer strips (MICRO-FLOOR "B" Removawell, Dynatech, Inc, Alexandria, VA) were coated with affinity-purified anti-human IgE (Kirkegaard Perry Labs, Gaithersburg, MD). Twenty nanograms of antibody in 100 μl of 60 mM carbonate/bicarbonate coupling buffer, pH 9.2, was added per well, incubated overnight at 4°C , and then removed by aspiration. To prevent nonspecific binding of other proteins, 300 μl /well of 0.1% Tween/PBS, pH 7.4, containing 0.1% Sodium azide, were added to the wells. The strips were stored at 4°C .

Before use, the wells were washed with PBS, pH 7.4, containing 0.05% Tween (PBS-TW). The sera were diluted twofold in 5% FCS/PBS, 50 μl added to quadruplicate wells, and incubated overnight at room temperature. The wells were washed four times with PBS/TW. One hundred nanograms of biotinylated anti-human IgE in 1% FCS/PBS was added per well and incubated for 1 hour at room temperature. The affinity purified anti-human IgE was biotinylated in a 1 : 1 molar reaction with biotinyl-*N*-hydroxysuccinimide.⁽⁴⁾ The wells were washed and 100 μl of a 1 : 5000 dilution of avidin-coupled alkaline phosphatase were added for 20 minutes. The wells were washed again followed by a 10-minute room temperature incubation, with mixing, with 100 μl /well of diethanolamine buffer, pH 9.8. After washing, the enzyme substrate, 100 μl of 10^{-4} M 4-methylumbelliferyl phosphate, was added and the resulting fluorescence was measured with a microfluorometer at intervals, from 2 to 60 minutes. The readings were transferred directly into a microcomputer for analysis.

Standard curves were constructed from appropriate dilutions of a patient serum that had been standardized against the U.S. reference standard.⁽⁵⁾ The average net fluorescent units produced by unknown samples were converted to units of IgE (IU) by calculation from the computer-fitted standard curve. Six internal standards were included with each assay.

Allergen-specific IgE was assayed (in a similar ELISA system) as previously reported.⁽³⁾ Briefly, the allergens of interest—cat, ragweed, *Alternaria*, timothy grass, dog, and house dust mite (*Dermatophagoides farinae*)—were diluted in buffer (60 mmol/liter carbonate-bicarbonate, pH 9.8) and absorbed onto the plastic microtiter strips overnight at 4°C . The strips subsequently were washed and blocked with 5% FCS-PBS. Aliquots of patients sera (50 μl) were then added

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to duplicate wells and incubated overnight. After washing, the wells were processed in the same manner as in the total IgE assay with the addition of anti-IgE, washes, enzyme, and substrate. A pool of sera lacking specific IgE for the allergens being studied but with a total concentration of IgE similar to that of the patient samples (negative control) was run in each assay. The results of the patient samples were expressed as the ratio between the mean fluorescence of the patient wells and the negative pool.

Records were obtained to collect the sex, date of birth, date of laboratory test, and test results. A value of 2 or more for an antigen-specific test, which is equal to the mean of the negative control pool plus 4 SD above the mean of the control pool in multiple assays, was considered a positive result. Subjects were classified into a high total IgE category, *e.g.*, the measured total IgE was 1 SD above the mean expected for age. Expected levels were based on a report from Scandinavia that measured age-specific total IgE levels in children without allergies.⁽⁶⁾ Using a Chi-square test, the month of birth of subjects was compared to the distribution of all births ($n = 58,777$) in the same geographic area (metropolitan Detroit, *i.e.*, Wayne, Oakland, and Macomb counties) in 1975, the midbirth year for the study population. The Edward's test for sinusoidality was used to test whether the children with high total or positive antigen-specific IgE demonstrated a seasonal pattern with respect to month of birth.⁽⁷⁾ These analyses were repeated adjusting the number of high values for the overall monthly distribution of births in the study sample.

RESULTS

Sera from a total of 631 children were included in the study, 334 (53%) were male. The mean age at testing was 8.8 years (1 SD = 4.8), with a range from under 1 to 18 years. The years of birth ranged from 1961 to 1985. Table 1 presents the percentage of children sensitive to the tested allergens. The highest proportion of children, 365 (58%) were sensitive to cat allergen, followed by ragweed, 267 (43%). The least commonly detected sensitivity was to house dust mite, $n = 202$ (32%). A total of 369 (59%) were categorized as having high total IgE. The frequency of children with very high antigen-specific IgE levels, ≥ 6 , varied from 7% for *Alternaria* to 16% for cat and ragweed.

Using the Chi-square statistic, no significant associations were found relating month of birth to any allergen-specific IgE or to total IgE. Figures 1–3 display the percent distribution by birth month of children with IgE specific for seasonal allergens compared to the general population. Among those with a positive test for IgE to timothy, the fewest children were born in May (Fig.

TABLE 1. DISTRIBUTION OF CHILDREN BY LEVEL OF TOTAL AND ANTIGEN-SPECIFIC IgE

Antigen	Number tested	Number positive ^a				Number high positives, ^b Total (%)
		Total	(%)	Males	Females	
Cat	626	365	(58)	187	178	103 (16)
Ragweed	628	267	(43)	147	120	101 (16)
Alternaria	440	161	(37)	101	60	29 (7)
Timothy	629	211	(34)	118	93	94 (15)
Dog	623	206	(33)	114	92	62 (10)
Mite	631	202	(32)	113	89	63 (10)
Total IgE	627	369 ^c	(59)	207	162	

^aNumber greater than two times the negative control sera.

^bNumber greater than six times the negative control sera.

^cNumber greater than 1 SD above mean for age of subject.

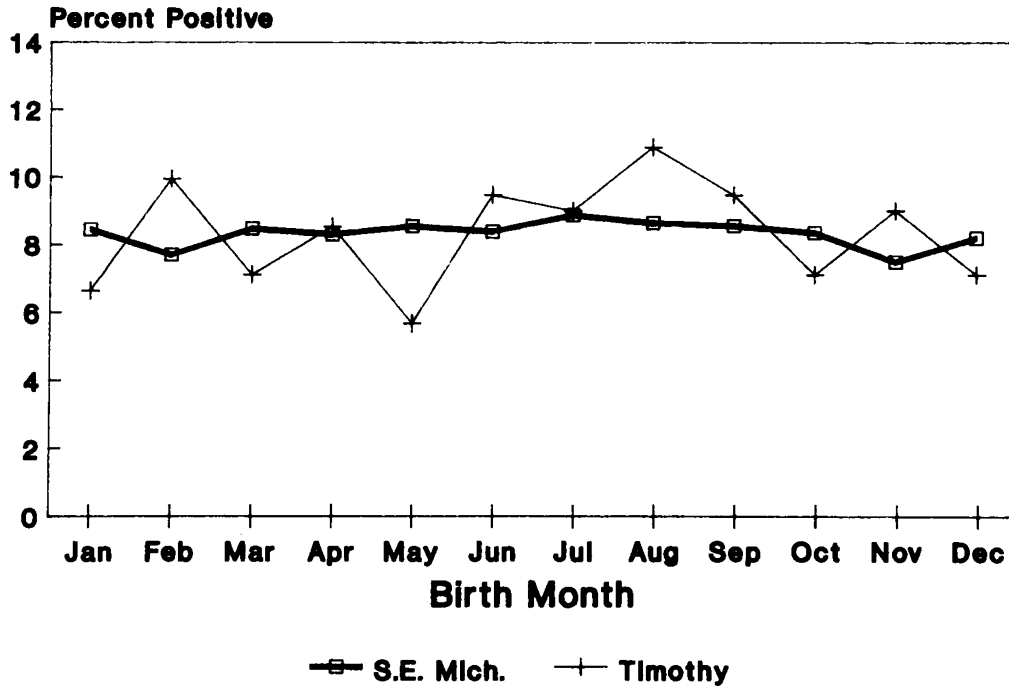


FIG. 1. Percentage distribution by birth month for children with sensitization to timothy ($n = 211$) and comparison group ($n = 58,777$)

1). Children who were 0–3 months of age during the May–June grass season were not statistically more likely to have a positive test for IgE to timothy ($p < 0.4$). Ragweed-positive children were born with a greater than expected frequency during the August–October ragweed season (Fig. 2), although the differences were not statistically significant. There was again no significant association with early exposure to ragweed measured by being 0–3 months of age during a ragweed season ($p > 0.7$). Sensitivity to mite was slightly more common among August and September births, which are the months when humidity is highest in the Detroit area (Fig. 3), but again the differences are not significant.

Figures 4–6 display the percent birth month distributions for the nonseasonal allergens. No trend was evident for cat sensitization (Fig. 4). A higher percentage of children sensitive to dog antigens were born in the summer (Fig. 5). Sensitization to the mold *Alternaria* showed a peak in July (Fig. 6). None of these relatively nonseasonal allergens were statistically associated with a different birth month pattern.

Stratifying for age and sex yielded only one statistically significant association; prepubescent girls (<12 years) with high IgE to dog deviated from expected ($p < 0.02$). They were less likely to be born in January and May and more likely in June and August, but no pattern relevant to exposure to dogs could be discerned. Figure 7 displays the birth months of subjects with a positive result to any one or more of the specific antigens. Again, this birth month distribution was not statistically different than expected ($p < 0.28$).

The Edward's test was performed for total IgE, each allergen-specific IgE, and for those with any positive specific IgE result, to detect sinusoidal periodicity, or a seasonal trend. No pattern was found to be statistically significant.

The analyses were repeated adjusting for the overall monthly distribution of births in the total study sample, and second, by restricting the subject group to the sequentially tested 442 children who were clinically suspected of having allergic disease and excluding those enrolled in the other study.⁽²⁾ There were no statistically significant differences in birth month distributions or seasonal

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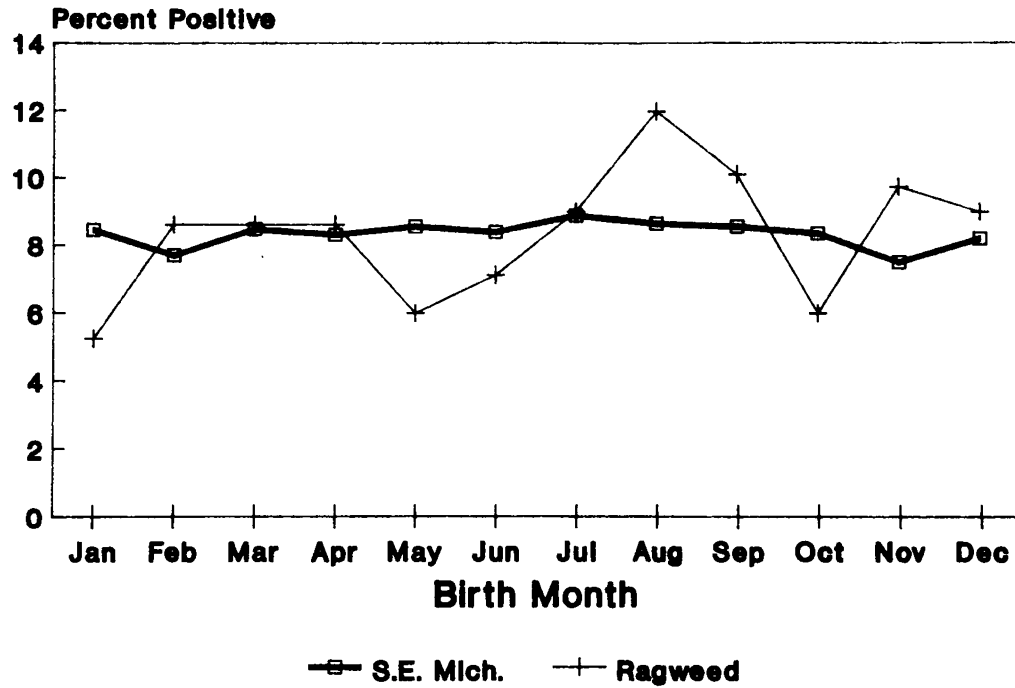


FIG. 2. Percentage distribution by birth month for children with sensitization to ragweed ($n = 267$) and comparison group ($n = 58,777$).

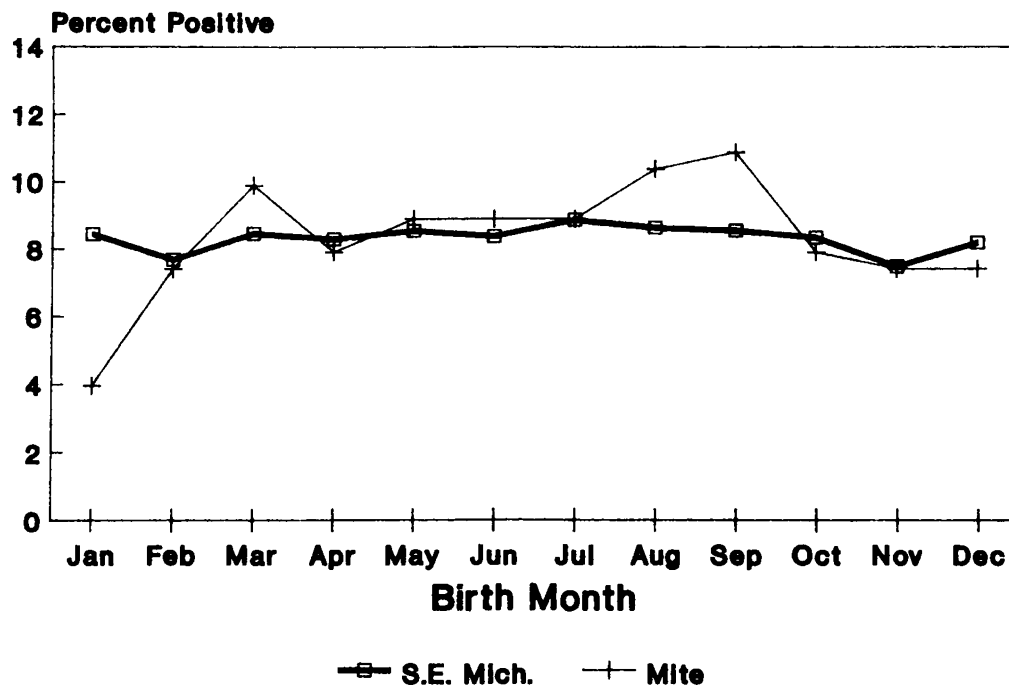


FIG. 3. Percentage distribution by birth month for children with sensitization to mite ($n = 202$) and comparison group ($n = 58,777$).

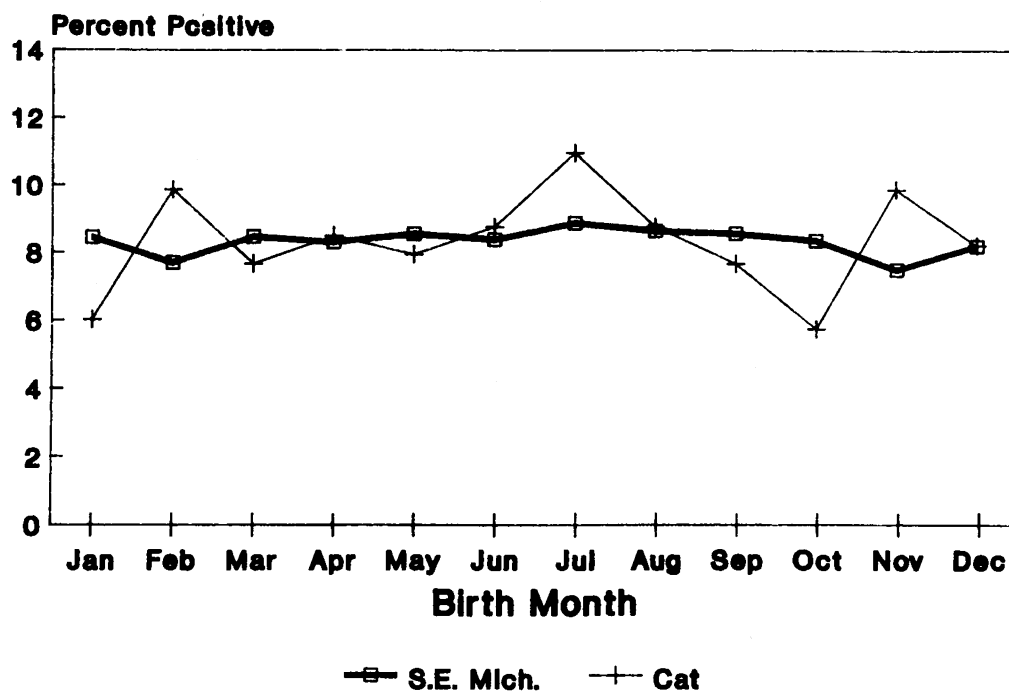


FIG. 4. Percentage distribution by birth month for children with sensitization to cat ($n = 365$) and comparison group ($n = 58,777$).

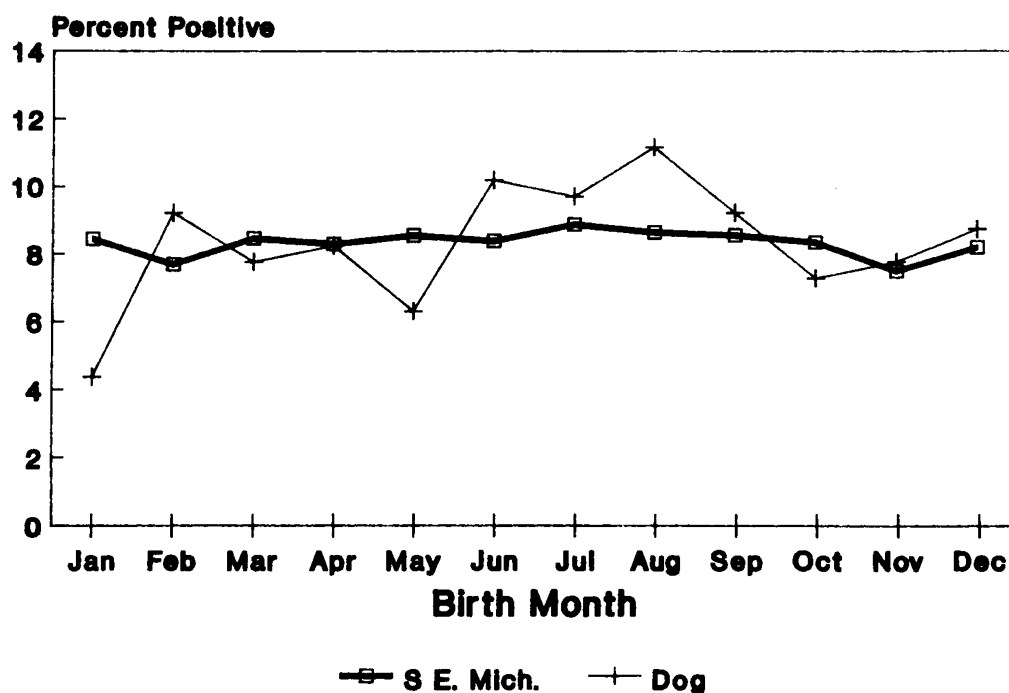


FIG. 5. Percentage distribution by birth month for children with sensitization to dog ($n = 206$) and comparison group ($n = 58,777$).

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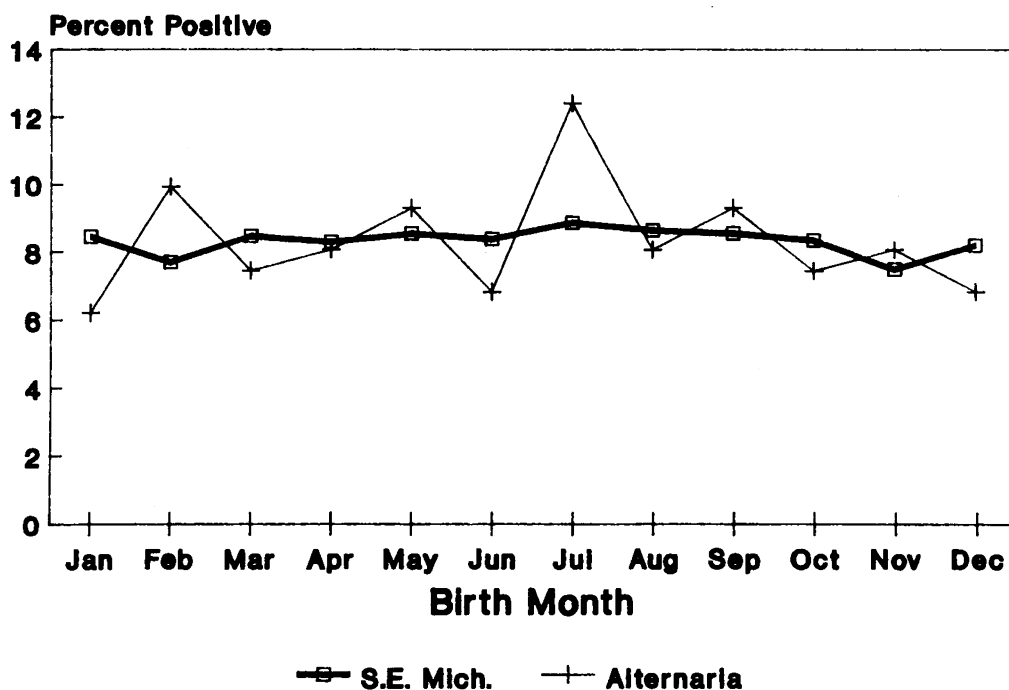


FIG. 6. Percentage distribution by birth month for children with sensitization to *Alternaria* ($n = 161$) and comparison group ($n = 58,777$).

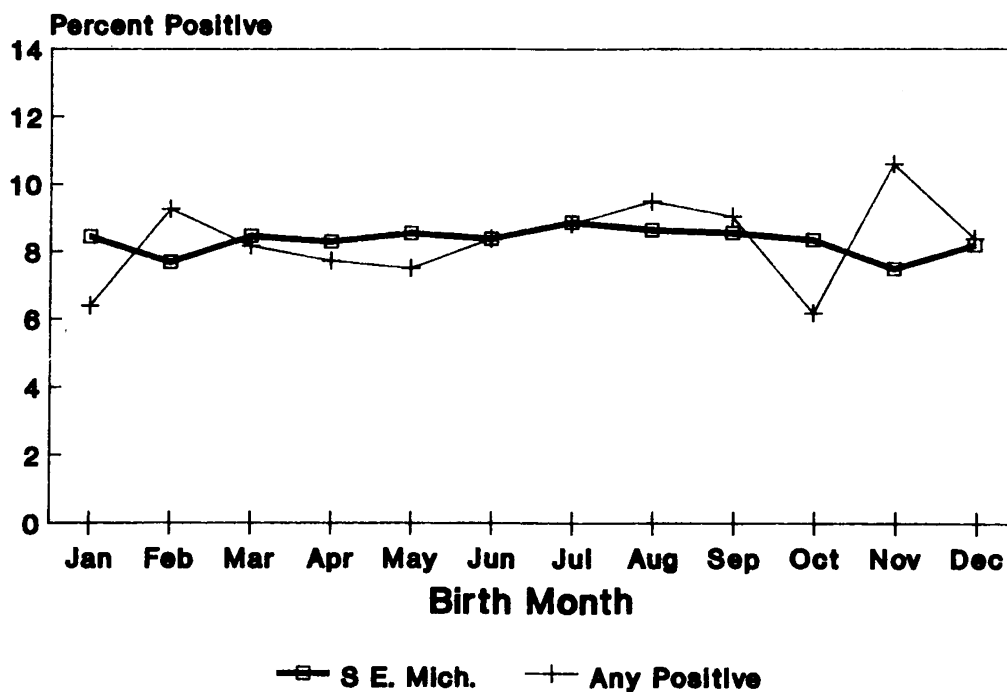


FIG. 7. Percentage distribution by birth month for children with sensitization to timothy, ragweed, mite, cat, dog or *Alternaria* ($n = 453$) and comparison group ($n = 58,777$).

trends. Chi-square and Edward's tests were additionally performed using the ≥ 6 cutpoint for antigen-specific IgE levels. The Chi-square was significant for IgE to cat ($p < 0.006$), with a marked peak in February and a drop in January; however, there was no evidence of a cyclic trend. There was a tendency for a cyclic trend in the birth month distribution of those with IgE ≥ 6 to dog ($p < 0.06$), with an increased number of births in the latter part of the year, however, the numbers were small. There was no other evidence of birth month patterns among subjects with antigen-specific IgE levels ≥ 6 .

DISCUSSION

The hypothesis that month of birth is a risk factor for the development of allergy is still unsettled. The substantial number of studies addressing this issue are reviewed in Table 2. Populations from many different geographical locations are included; the types and time of allergen exposures related to calendar time obviously would vary. Despite these differences, some consistent patterns are observed.

Our finding that ragweed allergic children were born more often than expected in the height of the ragweed season, while not statistically significant, is consistent with the concept that neonatal exposure to an antigen may increase the risk of developing hypersensitivity. A birth month pattern related to grass or tree pollen was not detected in this study, but a spring time preponderance is repeatedly demonstrated in other reports,^(9,15-17,23,24) with significant results. All of these studies included the month of April as part of a high-risk period. Reports that considered dust mite allergies, which were all northern hemisphere populations, generally found significantly more births in the summer and fall months.^(11,12,20,24) The birth month of September was found to be a high-risk month in each case, and all but one study⁽¹¹⁾ also included August as a high-risk month. In addition, our results support suggested findings from other work that people with allergy to animal epithelium are less likely to be winter babies.

The differences across studies may be due to the different criteria used to measure disease. One study, for example, showed no associations when using all patients with respiratory allergic disease in which a causative allergen had been identified, but significant trends emerged when the criteria were restricted to exclude those subjects with perennial symptoms.⁽¹⁰⁾ The present study is the only one in the series that used *in vitro* measurement of specific IgE as a measure of disease. Moreover, the age ranges of subjects were variable. As some reports revealed a dissipation of a birth month effect as age increased, those studies that analyzed all ages together may have masked birth month trends in the youngest groups.

If the time of birth is demonstrated to be related to allergen hypersensitivity, this factor has the potential for intervention through family planning for parents with a history of allergic disease. As population data for birth month is readily available, the usual problems associated with selecting a comparison population are avoided. However, repeated studies using similar disease and age criteria, and preferably using a defined population, are required to investigate this issue further. In addition, data regarding additional potential confounding variables besides age and sex, such as race, family history of allergies, and cord blood IgE levels, should optimally be considered in analyses.

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TABLE 2. RESULTS OF PREVIOUS STUDIES OF BIRTH MONTH AND ATOPIC DISEASE

<i>Location (ref.)</i>	<i>n</i>	<i>Age (year)</i>	<i>Disease criteria</i>	<i>High-risk birth months^a</i>
United States ⁽⁸⁾ 1975	210	not stated	Positive skin test to ragweed, trees, or grass pollen	None
Finland ⁽⁹⁾ 1976	1421	All	Therapy for pollen allergy	Mar-May*
	728	All	Positive skin test for animal epithelium	Apr-May**
England ⁽¹⁰⁾ 1977	476	Not stated	Clinical allergy to grass pollen	Dec-Feb***
England ⁽¹¹⁾ 1978	58	<2	Positive skin test to house dust mite, eczema, family history of allergy	Sep-Oct*
England ⁽¹²⁾ 1978	85	5-14	Asthmatic, positive skin test to house dust mite	Aug-Dec*
England ⁽¹³⁾ 1979	1715	5-15	Asthma diagnosis	May-Oct*
Australia ⁽¹⁴⁾ 1979 ^b	86	3-14	Clinical symptoms of allergy, positive skin test to ≥ 1 of 6 antigens	None
Finland ⁽¹⁵⁾ 1980	2171	0-29	Positive skin test to birch pollen	Feb-Apr*
Finland ⁽¹⁶⁾ 1981	605	15-17	Positive skin test and clinical allergy to pollen	Dec-May**
Finland ⁽¹⁷⁾ 1981	4225	0-29	Positive skin test to grass pollen	Apr-May*
	2870	0-29	Positive skin test to mugwort pollen	Apr-May*
	1360	0-19	Positive skin test to animal epithelium	Sep-Oct
England ⁽¹⁸⁾ 1981	2483	1-4	Asthma hospital admissions	Oct-Nov*
	3272	5-14	Asthma hospital admissions	Oct-Nov*
New Zealand ⁽¹⁹⁾ 1983 ^b	1571	0-14	Asthma hospital admissions	Jun-Jul
Denmark ⁽²⁰⁾ 1983	240	Adults	Asthma or rhinitis and positive skin test to house dust mite	May-Sep*
	336	Adults	Asthma or rhinitis and positive skin test to grass pollen	None
England ⁽²¹⁾ 1985	4520	<16	Hospital diagnosis of asthma	Sep-Jan*
Sweden ⁽²²⁾ 1986	119	7	Clinical atopic disease, high cord IgE	May*
Italy ⁽²³⁾ 1986	207	All	Positive skin test to grass pollen, seasonal asthma, and rhinitis	Mar-Jun*
Italy ⁽²⁴⁾ 1988	1685	1-14	Positive skin test and/or RAST only to mites	Jun-Sep*
	439	1-14	Positive skin test and/or RAST only to grass pollen	Mar-May*
Detroit 1988 (current study)	211	0-18	Positive IgE to grass	None
	267	0-18	Positive IgE to ragweed	Aug-Oct
	202	0-18	Positive IgE to house dust mite	Aug-Sep
			Positive IgE to dog epithelium	Jun-Sep
			Positive IgE to cat epithelium	None

*Statistically significant findings reported; **significant findings for males only; ***significant findings for females only.

^bSouthern hemisphere, therefore opposite seasonal patterns expected.

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