

Before-birth climatologic data may play a role in the development of allergies in infants

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While an exacerbation in allergic symptoms corresponding to seasons has long been reported, few studies have investigated the association between the season of birth and allergic disorders. The aim of this study was to investigate whether the climatologic data before and after birth affected the incidence of atopic dermatitis (AD) and the results of allergy-related blood tests in early infancy. From February 1995 to January 2000, 2136 infants were tested for AD and followed for 12 months. AD patients were tested by using allergy-related blood tests. Data were compared according to the month of birth and the climatologic data using a computed statistical software package. Six hundred and thirty infants had AD before 12 months old, and significant differences were found according to the season of birth ($p < 0.0001$). Infants born in spring showed the lowest (22.3%) incidence, while those born in autumn showed the highest (34.6%). In 369 patients, total serum IgE levels, and serum specific IgE levels with egg white at 3 months old were also different according to the season of birth. All of these levels were lower in patients born in spring and summer, and higher in patients born in autumn and winter. Furthermore, the cumulative sunshine amount during the 3 months before and after birth was inversely correlated, while the average temperature over the 3 months before birth was positively correlated to the incidence of AD according to the month of birth. The climatologic data around birth may play an important role in whether an infant develops allergies.

Kazuyo Kuzume¹ and Masahito Kusu²

¹Department of Pediatrics, Ehime University School of Medicine, Toon, Japan, ²Kusu Children's Clinic, Matsuyama, Japan

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Kazuyo Kuzume, Department of Pediatrics, Ehime University School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan

Tel.: 81 89 960 5320

Fax: +81 89 964 9131

E-mail: kuzumeka@m.ehime-u.ac.jp

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Although the incidence of allergic diseases in Japanese children has increased dramatically, more than doubling over past 20 yr (1), little attention has been paid to the possible role of the season of birth in allergic diseases.

In several diseases, such as schizophrenia (2), insulin-dependent diabetes (3), and allergic disorders (4–8), a relationship between the incidence and the season of birth has been observed. Pollen-allergy sensitization or desensitization may be caused by perinatal exposure to pollen (4–6) and some studies have shown that the incidence of atopic dermatitis (AD) varies according to the season of birth (7, 8). Exacerbation of AD symptoms in winter is also known to occur (9). Seasonal weather may also be important in the development of allergic disorders. An experimental study has

demonstrated that low humidity caused epidermal proliferation and mast cell hypertrophy and degranulation in disrupted animal skin (10). On the other hand, exposure to UV light induces epidermal thickening (11) and phototherapy is useful for restoring the skin barrier in atopic dermatitis (12). Thus, weather conditions may affect the development of atopic dermatitis. Early infancy seems to be the most important period for allergy sensitization (6, 13), but it is unknown whether the season of birth is an environmental risk factor or whether it influences the incidence of allergic diseases or the results of allergy-related examinations (5, 14). In addition, some studies show that the season of birth may affect total IgE levels (15, 16), interleukin (IL)-10 levels (17) or T-cell activity (18) in umbilical cord blood.

We hypothesized that the season during which a baby was born would influence the incidence of allergy-related diseases. From 1995 to 2000, we examined 2136 infants from birth to 12 months of age and observed the relationship between the season of birth and the incidence of atopic dermatitis by testing their total serum IgE levels and their serum specific IgE levels. We found the incidence of atopic dermatitis, the total serum IgE levels and the serum specific IgE antibody levels for egg white in AD patients were lower in infants born in spring and summer compared with those born in autumn and winter. Also, the cumulative sunshine amount before and after birth correlated inversely to allergic expression. We therefore conclude that the season of birth relates to the incidence of allergic diseases and influences the results of allergy-related blood tests.

Subjects and method

From February 1995 to January 2000, 3530 babies were born in NTT Nishinohon Matsuyama Hospital. Babies whose families did not utilize the hospital's well-baby clinic for follow-up care were excluded. This left an initial population of 2855. Of these, 719 patients dropped out, leaving 2136 (1087: male, 1049: female) infants. All of them lived in Matsuyama city or its vicinity and the number of infants was equal to about 9% of the whole birth population of this area during that period. These infants were examined at birth and at 1, 3, 6, 9, and 12 months of age, and 630 AD patients were identified. A subpopulation of 369 patients with AD was selected for further study and followed in the allergy clinic of NTT Nishinohon Matsuyama Hospital. Because NTT Nishinohon Matsuyama Hospital is not a research institution, no regular institutional review board was available. However, patients' families were informed individually by the physician and written consent was obtained from parents.

The diagnosis of atopic dermatitis was made according to the criteria of Leung, which modified the definition of AD presented by Hanifin and Rajka (19). A questionnaire ascertained data regarding the nutrition, siblings, and familial history of allergy. A positive family history of allergy was defined as a case whose parents, siblings, or both had major allergic diseases, bronchial asthma, allergic rhinitis, allergic conjunctivitis, or atopic dermatitis. All diagnoses were made by the same pediatric allergist.

Each year was divided into four seasons: spring, from March to May; summer, from June

to August; autumn, from September to November; and winter, from December to February. Cases were tallied in each season to evaluate the differences among seasons of birth. We also tracked the average temperature and humidity and the cumulative precipitation and sunshine amounts for the 3 months before and after birth, as indicators of climate conditions. Our climate-condition data were obtained from the weather bureau in Matsuyama.

To determine the seasonal variation in allergies, we followed 369 AD patients and examined them by peripheral eosinophil count, total serum IgE levels, and by serum specific IgE antibody levels using the Pharmacia CAP System FEIA (CAP-RAST: Pharmacia Diagnostics, Sweden) with egg white, milk, and house dust mite (*Dermatophgoides pteronyssinus*) at 3 months of age.

Data were analyzed by using a personal computer statistical software package (SPSS 13.0j; SPSS Japan Inc., Tokyo, Japan). The cumulative incidences of AD before 12 months old according to the season of birth were compared by using the chi-squared test and odds ratios were calculated. The differences of allergy-related blood tests levels in AD patients were analyzed according to the season of birth, using the Kruskal–Wallis test with Dunn's multiple comparison test. To evaluate relationships between allergic symptoms or allergy-related blood test data and the local weather data, the monthly incidence of AD and the logarithm of averaged total serum IgE levels and averaged CAP-RAST levels with egg white in AD patients according to the month of birth were compared to the local climate data over the 3 months before and after birth by using multiple regression analyses. Comparisons were considered significant at a p -value < 0.05 . Data were expressed as the percentage or median (range).

Results

There were 630 cases (29.5%) of AD patients observed in 5 yr. In these cases, 366 (58.1%) were male and 264 (41.9%) were female. Furthermore, 401 cases (64.0%) had positive family history of allergy. The results showed that the incidence of AD was significantly different among the season of birth (shown in Table 1). The incidence of AD was lowest (22.3%) in infants born in the spring and highest (34.6%) in those born in the autumn. In infants born in the spring, the odds ratio (OR) was 0.6092 and the confidence interval (CI) was from 0.4860 to 0.7637. In infants born in the autumn, the OR was 1.366 (CI, 1.106–1.688). As other studies had shown that incidences of

Table 1. The incidence of atopic dermatitis (AD) symptoms and background features according to the season of birth

	Season of birth				p-value
	Spring	Summer	Autumn	Winter	
% of AD patients	22.3	27.4	34.6	34.0	<0.0001
spring vs. others		OR 0.6092 (CI 0.4860–0.7637)			<0.0001
autumn vs. others		OR 1.366 (CI 1.106–1.688)			0.0044
winter vs. others		OR 1.328 (CI 1.078–1.636)			0.009
% of male infants	48.4	49.9	52.3	53.0	0.3863
% of positive-family-history cases	49.2	47.3	48.9	48.1	0.9368
% of first delivered child	60.6	63.5	62.4	66.7	0.1970
% of breast and combined feeding	64.9	59.0	65.1	63.4	0.1675

Undesignated numbers present the percentage. P-values were calculated with chi-square test.

Spring (n = 556), Summer (n = 521), Autumn (n = 518), Winter (n = 541).

OR, odds ratio; CI, confidence interval.

allergic diseases and SPT-positive rate (7, 20) were higher for male, positive-family cases, first-delivered children, and infants who were formula-fed, we gathered data for these factors. We found no differences among the season of birth for any of these factors (shown in Table 1).

In the 369 AD cases that were observed in our allergy clinic and regularly tested, the total serum IgE levels and the CAP-RAST levels with egg white at 3 months old showed significant differences among the season of birth (shown in Table 2). The total serum IgE levels and the CAP-RAST levels with egg white were lower in infants born in the spring and the summer, while higher in those born in the fall and the winter. Although the peripheral Eosinophil counts were also lower in patients born in spring and summer and higher in autumn and winter, but significant difference in the peripheral Eosinophil counts was not found according to the season of birth ($p = 0.0648$). As the CAP-RAST levels with cow's milk and house dust mite were rarely positive in those patients, the further evaluations of these data were excluded from the present study.

According to the multiple regression analysis, there were significant inverse correlations

between the incidence of AD according to the month of birth and the cumulative sunshine amount over the 3 months before and after birth, whereas the average temperature during the 3 months before birth were positively correlated to the incidence of AD according to the month of birth. Additionally, climatologic data before birth showed the similar effects on subjects with the positive family history of allergic diseases (Table 3). Also, the logarithm of the averaged total serum IgE levels and the logarithm of the averaged CAP-RAST levels with egg white in AD patients at 3 months of age presented a similar significant relationship to the cumulative sunshine amount or the average temperature (Table 4). The average humidity and the cumulative precipitation during the 3 months before and after birth did not show any significant relationship to the incidence of AD or allergy-related blood test levels in AD patients (data are not shown).

The incidence of AD according to season of birth, the cumulative sunshine amount, and the average temperature over the 3 months before birth according to season of birth were graphed in Fig. 1.

Table 2. The results of allergy-related blood test in atopic dermatitis (AD) patients at 3 months of age according to the season of birth

	Season of birth				p-value
	Spring	Summer	Autumn	Winter	
Total serum IgE levels (IU/ml)*	7.8(2.0–63)	5.0(1–47)	8.3(1–200)	8.5 (1–160)	0.0018
CAP-RAST with egg white levels (U _A /ml)†	0.34 (0.34–9.0)	0.34 (0.34–2.16)	1.17 (0.34–15.97)	0.77 (0.34–17.17)	<0.0001

Values are given as median (range).

* $p < 0.01$, summer vs. autumn and summer vs. winter.

† $p < 0.001$, summer vs. autumn; $p < 0.01$, summer vs. winter.

P-values were evaluated using Kruskal–Wallis test with Dunn's multiple comparison test.

The peripheral Eosinophil counts did not show significant difference according to the season of birth.

Spring (n = 50), Summer (n = 81), Autumn (n = 118), Winter (n = 120).

CAP-RAST levels, serum-specific IgE antibody levels by using the Pharmacia CAP System FEIA.

Valuable A	Valuable B	Beta weight	Significance (p)
% of AD in total cases	Before birth	Cumulative sunshine amounts	
		–1.009	<0.001
	After birth	–0.460	0.028
		Average temperature	
% of AD in positive-family-history cases	Before birth	1.228	0.009
		–0.094	0.837
	After birth	Cumulative sunshine amounts	
		–0.819	0.001
	After birth	–0.370	0.100
		Average temperature	
	Before birth	1.542	0.002
		0.943	0.862

A positive-family-history case was defined as a case whose parents, siblings, or both had major allergic diseases, bronchial asthma, allergic rhinitis, allergic conjunctivitis, or atopic dermatitis. (total cases, $n = 2136$; positive-family-history cases, $n = 1097$).

The percentages of AD patients were calculated according to the month of birth and compared with the climatologic data over 3 months before and after birth ($n = 60$, 12 months $\times$ 5 yr).

There were no significant relationship between average humidity or cumulative precipitation and each percentage.

Valuable A	Valuable B	Beta weight	Significance (p)
Logarithm of total serum IgE levels	Before birth	Cumulative sunshine amounts	
		–0.936	<0.001
	After birth	–0.374	0.056
		Average temperature	
Logarithm of CAP-RAST with egg white levels	Before birth	1.378	0.004
		–0.240	0.580
	After birth	Cumulative sunshine amounts	
		–1.020	<0.001
	After birth	–0.667	0.001
		Average temperature	
	Before birth	1.507	0.001
		0.078	0.854

The logarithm of total serum IgE levels and CAP-RAST levels with egg white in AD patients ($n = 369$) were averaged according to the month of birth and compared with the climatologic data over 3 months before and after birth ($n = 60$, 12 months $\times$ 5 yr). There were no significant relationship between average humidity or cumulative precipitation and each levels.

Table 3. The relationship between the incidence of atopic dermatitis (AD) in total cases or the incidence of AD in positive-family-history cases and the climatologic data over 3 months before and after birth using the multiple regression analysis

Table 4. The relationship between the results of blood test in atopic dermatitis (AD) patients according to the month of birth and the climatologic data over 3 months before and after birth using the multiple regression analysis

Discussion

We found a seasonal variation in the incidence of AD before 12 months of age and in the total serum IgE and CAP-RAST levels with egg white in the AD patients at 3 months of age, according to the season of birth. These allergic appearances according to the month of birth showed a significant inverse correlation to the cumulative sunshine amounts over the 3 months before and after birth. Also, the average temperature during the 3 months before birth had a significant positive correlation to the AD incidence and the allergy-related blood test levels in AD patients.

The incidence of atopic dermatitis in infants has been reported as between 10% and 20% from cross-sectional studies in Japan (21, 22). Because the present study was performed by

using prospective methods and diagnosed by a physician directly instead of using questionnaires, our results showed a higher incidence of atopic dermatitis before 12 months of age when compared with these reports. Although a prospective study is preferable for investigating the incidence of diseases, prospective reports about atopic dermatitis or allergy-related examinations are rare. The present study is also the first prospective study reported from Japan.

A seasonal variation in AD symptoms has been reported since 1940 (23), and the relationship between the allergic manifestations and season of birth has been reported (4–8, 14, 24, 25). While Schäfer (1993) found no relationship between the results of skin prick test and patient's month of birth (25), the few other studies on the issue do show seasonal variation in

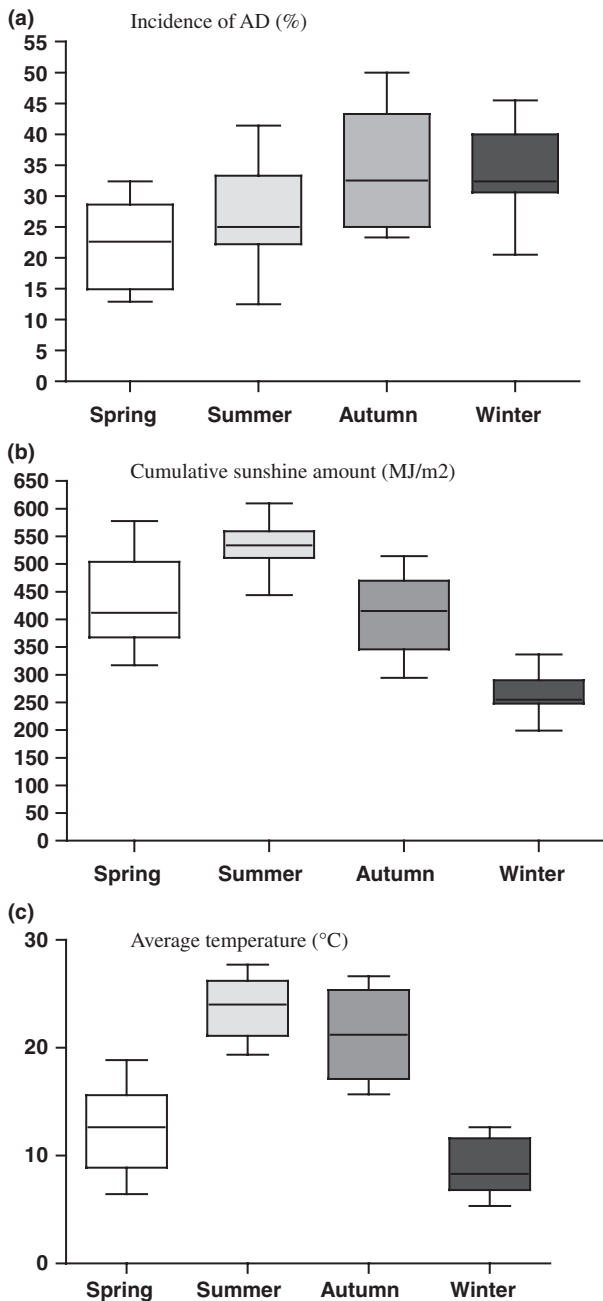


Fig. 1. (a) The percentage of the atopic dermatitis (AD) according to the month of birth during 5 yr divided into four seasons: spring, from March to May ($n = 556$); summer, from June to August ($n = 521$); autumn, from September to November ($n = 518$); winter, from December to February ($n = 541$). Significance: $p < 0.001$, spring vs. autumn and spring vs. winter, $p < 0.05$, summer vs. autumn and summer vs. winter. (b) The cumulative sunshine amount (MJ/m², mega-joules/m²) for 3 months before birth divided into four seasons according to the same way as Fig. 1a. Significance: $p < 0.001$, winter vs. summer, winter vs. spring, winter vs. autumn, summer vs. autumn, and spring vs. summer. (c) The average temperature (°C) over 3 months before birth divided into four seasons according to the same way as Fig. 1a. Significance: $p < 0.001$, winter vs. summer, winter vs. autumn, winter vs. spring, spring vs. summer, and spring vs. autumn; $p < 0.05$, summer vs. autumn.

the incidence of allergic diseases (4–8, 14, 24). A long-term prospective study from Sweden (5) showed that the incidence of allergic diseases and the serum-specific IgE antibodies against multi-allergens were lowest in children born in spring. It seems reasonable that the incidence of tree-pollen allergy (4, 6) and serum-specific IgE levels for tree-pollen (6) are lower in infants born in spring and summer, as the tree-pollen exposure decreases during those seasons. But, interestingly, in a large study of the specific IgE levels in allergic patients, there was also a significant seasonal variation not only in seasonal allergens, but also in non-seasonal allergens (14). According to this study, the specific IgE levels for egg white in allergic patients under 4 yr old were lowest in those born in May. Further, even a report from the tropics, where there is little seasonal variation in climatologic data, showed an incidence of asthma that varied in a seasonal pattern (24). The relationship between allergic manifestation and season of birth seems to be influenced not only by the allergen exposure, but also by the other environmental factors.

A cross-sectional study of allergic diseases in school children from Japan reported that the incidence of atopic dermatitis varies depending on the season of birth, and, like the findings in the present study, it was lowest in those born in spring and highest in autumn (8). This study also showed that the water-holding capacity of uninvolved skin in children with AD was lower than that in control subjects (8). Kusunoki et al. speculated that low humidity in early infancy damaged the skin barrier in children, and as a result they developed AD symptoms because of induced production of inflammatory cytokines and increases in the antigen-presenting ability in skin Langerhans cells (8). The other report, from the Netherlands, showed that in AD patients, the transepidermal water loss with the repeated application of sodium lauryl sulfate was greater in November, and the sensitivity to intradermal skin tests with bioactive agents (such as codein, histamin, and substance P) was higher in November compared with those in July (26). They hypothesized that low humidity and decreased exposure to UV light effected these seasonal changes in the skin of AD patients. Furthermore, in one animal study, Denda (1998) observed that the exposure to the low humidity amplified the DNA synthesis responding to barrier disruption, resulting in epidermal hyperplasia, as well as hypertrophy and degranulation in dermal mast cells (10). Temperature may also play a role, but this is not well defined. Low temperature has been known to cause urticaria (27), but cooling

temperatures abolish itch in patients with AD (28). Experimental studies showing that low temperatures induce or exacerbate atopic dermatitis have not been reported.

We found a striking relationship among the incidences of AD before 12 months of age and the climatologic data. The cumulative sunshine amount over the 3 months after birth presented a significant inverse correlation to the incidence of AD in total cases, according to the month of birth. Moreover, in AD patients, the total serum IgE levels and CAP-RAST with egg white, non-seasonal allergen, levels, showed the same relationship to the cumulative sunshine amount. As, in most patients, AD symptoms are observed during the period from 2 to 3 months of age, it seems reasonable that the climatologic conditions during the period before 3 months of age affect the development of AD symptoms and allergy-related blood test levels. We assume that the infants born in autumn and winter spend their early infancy in a season that is characterized by little sunshine. As epidermal thickening, which alleviates AD symptoms, is induced by the exposure to UV light (11), young infants born in autumn and winter may lose their skin barrier, because of weather condition. Also, early infancy is known to be an important period for allergy sensitization (6, 13). Together, these factors may prompt the development of AD symptoms. Interestingly, the sunshine amounts before birth showed an inverse correlation and the average temperature before birth had a positive correlation to the incidence of AD and allergy-related blood test levels in AD patients according to month of birth in the present study. To minimize the effects of family history of allergic diseases, we calculated the incidence of AD in the positive-family-history cases separately, compared them with the climatologic data over 3 months before and after birth, and found similar results. The fetus in the uterus may be influenced by climate conditions experienced by the mother and prepare to develop allergic symptoms after birth. The umbilical cord blood IgE has been reported to be lower in infants born in spring (29) and Zitterann A et al. (17) reported that the levels of 25-hydroxyvitamine D and immunosuppressive cytokine IL-10 in cord blood were higher in infants born in summer time compared with those born in winter time. As the cord blood IgE level is highly affected by the mother's total serum IgE (30), the high amount of sunshine and the relatively cool temperature in spring may modify intrauterine environments enough to suppress the development of allergic disorders.

In summary, we presented significant correlations between season of birth and AD manifestations. Also, there was a significant relationship between AD symptoms and sunshine amounts not only after birth, but also before birth. AD may be an important indicator of other serious allergic diseases. Once the reason for the varying incidence of AD according to the season of birth is determined, it may be possible to prevent allergy development. Also, clarifying the seasonal variation seen in the serum-specific IgE for the food allergens might be useful for treatment of food allergy.

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