

Month of birth and prevalence of atopic dermatitis in schoolchildren: Dry skin in early infancy as a possible etiologic factor

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Background: Month of birth has been shown to affect later development of allergic diseases.

Objective: We sought to evaluate the relationship between month of birth and the prevalence of atopic dermatitis (AD) in a large-scale general population of schoolchildren and to elucidate the possible mechanism for this relationship.

Methods: Questionnaire data on the prevalence of allergic diseases were obtained for 33,725 schoolchildren aged 7 to 15 years. In a separate study the water-holding capacity of "uninvolved" skin was compared for children with and without AD.

Results: We found striking differences in the prevalence of AD according to the month of birth ($\chi^2 = 34.9$, $P < .0001$). Overall, those born in autumn showed the highest (7.5%), and those born in spring showed the lowest (5.5%), prevalence of AD. There was little or no such tendency for the prevalence of bronchial asthma ($\chi^2 = 17.2$, $P = .103$) and allergic rhinitis ($\chi^2 = 24$, $P = .01$). We found no statistical variation across birth month in the ratio of AD with no other allergic disease/total AD, indicating that this deviation was observed whatever the allergic predisposition of the subjects. In a separate study a significantly lower water-holding capacity of uninvolved skin was observed in children with AD even from early infancy.

Conclusion: These findings lead us to speculate that the climate in early infancy affects the skin condition and that those born in autumn have dry skin in early infancy, which may ultimately result in a higher prevalence of AD among young schoolchildren. This might be at least one of the "nonallergic" etiologic factors of this complex disease. (*J Allergy Clin Immunol* 1999;103:1148-52.)

Key words: Atopic dermatitis, allergy, dry skin, epidemiology, month of birth, water holding capacity

Studies of the relationship between season of birth and allergy have indicated that early infancy seems to be of particular importance for later development of allergic diseases.¹⁻⁷ Most of these studies have shown that birth in winter is associated with a higher incidence of allergy. The reasons for this phenomenon might include more extended early exposure to an indoor environment during the longer and cooler winter period, which might involve more exposure to indoor allergens, or increased risk of

Abbreviations used

AD: Atopic dermatitis
AR: Allergic rhinitis
BA: Bronchial asthma
CI: Confidence interval
OR: Odds ratio

respiratory syncytial virus infection enhancing atopy during these months.⁷ Aalberse et al⁴ showed that this "horoscope" effect held not only for seasonal but also for nonseasonal allergens, such as egg white and cow's milk, and suggested a contribution by another unknown factor in addition to allergen exposure.

Atopic dermatitis (AD) is a major allergic disorder, especially in children,⁸ and its etiology involves both allergic predisposition and nonallergic environmental factors, such as seasonal climate changes, chemical irritants, bacterial colonization, and psychologic stress. So far, several reports have evaluated the relationship between month of birth and AD, and no significant differences in AD prevalence according to month of birth has been observed.^{9,10} However, these previous reports may have been biased because they targeted only rather small numbers of outpatients with AD. In this report we administered a large-scale questionnaire survey on the prevalence of allergic diseases among a general population of more than 30,000 children of elementary and junior high school age. We identified a relationship between month of birth and presence of allergic disease and found a much greater difference in the prevalence of AD according to the month of birth than of other allergic diseases. We hypothesized that dry skin and subsequent skin barrier disruption in the first several months of life was one of the reasons for these differences. This hypothesis was supported by a separate study in which the water-holding capacity of the "uninvolved" skin of children with AD was shown to be lower than that of children without AD.

METHODS

Epidemiologic studies on the prevalence of allergic diseases in schoolchildren

A questionnaire survey on the prevalence of 3 allergic diseases (ie, bronchial asthma [BA], allergic rhinitis [AR], and AD) was administered to schoolchildren aged 7 to 15 years. The questionnaire was based on that of the International Collaborative Study of Asth-

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ma and Allergies in Childhood (ISAAC)¹¹ and was prepared by the Study Group of Epidemiology of Allergic Diseases founded by the Japanese Ministry of Public Health and Welfare in 1993. Briefly, BA was defined as repeated episodes of wheezing with dyspnea during the preceding 2 years. AD was defined as chronic eczema with more than 3 of 9 symptoms (listed in Table I) typical of AD. This criteria was established by well-experienced dermatologist/allergologists in the study group and was validated by the group. AR was defined as the presence of more than 3 of the following chronic nasal symptoms: sneezing, rhinorrhea, scratching around the nose, and nasal obstruction. The questionnaire was distributed through schoolteachers to the parents of 56,108 Japanese schoolchildren aged 7 to 15 years in 133 randomly selected schools in the suburban areas of Kyoto, Japan. A total of 50,086 questionnaires, which covers approximately 17% of all schoolchildren in the area, was recovered (recovery rate, 89.3%). Among them, 33,725 subjects (67.3%) with the date of birth entered were analyzed for this study.

Water-holding capacity of uninvolved skin

The water-holding capacity of the uninvolved skin was evaluated by a skin impedance meter, as originally described by Tagami et al.¹² Seventy-two patients with AD (male:female, 39:33; mean age $\pm$ SD, 3.2 ± 3.9 years) who fulfilled the criteria of Hanifin and Rajka¹³ were randomly selected from among our outpatients. Sixty-four control subjects (male:female, 30:34; mean age $\pm$ SD, 5.7 ± 4.7 years) who had no history of any allergic disease or present illness were also chosen from outpatients visiting our clinic. Subjects with fever were excluded from the study because their fever may have affected the analysis. Subjects were allowed to remain quiet in a room with constant air conditions (temperature, $26^\circ\text{C} \pm 0.6^\circ\text{C}$; humidity, $57\% \pm 3.3\%$) for at least 20 minutes. Sensors were placed on the noneczematous skin of the forearm, abdomen, and back, and skin conductance was measured with a skin impedance meter kindly provided by Kao Corporation (Tokyo, Japan). The measurement was repeated 5 times for the same site, and 3 values, not including the maximum and minimum, were averaged. Data was rejected when subjects were crying or sweating.

Statistical analysis

Data was entered into a computer file (SPSS PC+ V4, Chicago, Ill). Chi-square analysis was used to analyze differences in the prevalence of allergic diseases. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with logistic regression analysis. In this analysis we tested whether the disease prevalence of those born in one season is significantly different from that of those born in the other 3 seasons combined. We did the same analysis for all 4 seasons independently, and the results were summarized in Tables II and III. The Mann-Whitney *U* test was used to analyze the difference in water-holding capacity between the skin of atopic and nonatopic children. Probability (*P*) values of less than .05 were considered to be statistically significant.

RESULTS

Month of birth and prevalence of allergic diseases

Striking variations were found in the prevalence of AD according to the month of birth. Fig 1, *a*, shows a clear downward bell-shaped distribution, reaching a minimum in May (5.2%, OR: 0.77, CI: 0.65-0.92, *P* = .003) and a maximum in November (7.6%, OR: 1.20, CI: 1.03-1.39, *P* = .017). The chi-square test showed that this variation according to month of birth was statistically significant ($\chi^2 = 34.9$, *P* < .0001). The same tendency was observed, but

TABLE I. List of symptoms for diagnosis of AD

Number	Symptom
1	Dry skin on the face
2	Red papules on the trunk
3	Red papules on the extremities
4	Dry skin on the trunk
5	Moist eczema on the flexor side of elbow joint
6	Lichenification on the flexor side of elbow joint
7	Moist eczema on the flexor side of knee joint
8	Lichenification on the flexor side of knee joint
9	Nummular eczema distributed over the body

with much less significance, for the prevalence of AR ($\chi^2 = 24.0$, *P* = .01), and there was no statistical significance for the prevalence of BA ($\chi^2 = 17.2$, *P* = .103) (Fig 1).

The subjects were divided into 4 groups according to the season of birth, and simple logistic regression analysis was performed. Those born in autumn (October to December) showed the highest (7.5%, OR: 1.22, CI: 1.01-1.34, *P* < .0001), and those born in spring (April to June) showed the lowest (5.5%, OR: 0.79, CI: 0.71-0.88, *P* < .0001), prevalence of AD (Table II). Again, no significant deviation according to the season of birth was observed for the prevalence of BA or AR (Table II). The association between birth in spring and autumn and the prevalence of AD remained significant (*P* = .0001 for birth in spring and *P* = .0004 for birth in autumn) after controlling for age, gender, association of other allergic diseases, and order of birth among siblings by using multiple logistic regression analysis. Variation in the prevalence of AD according to season of birth was still significant (*P* < .0001) when we analyzed AD prevalence in each season by treating it with 3 dichotomous variables, with autumn as the reference season.

Month of birth and prevalence of AD

Comparison between AD with "high" and "low" allergic predisposition. Although AD is one of the allergic diseases, its etiology involves not only allergic predisposition but also nonallergic environmental factors. Each patient is different in terms of the prevalence and importance of these factors. In this respect we assume that patients with AD without other allergic diseases, such as allergic asthma or allergic rhinitis, have less allergic predisposition than those with any other allergic diseases. Therefore we defined AD accompanied by neither present illness nor a past history of any other allergic diseases as AD with "low allergic" predisposition. We checked whether there was any seasonal variation in the ratio of low allergic AD/total AD. We found no significant variation in such a ratio ($\chi^2 = 5.1$, *P* = .93), indicating that children born in spring tend to have a lower frequency of AD than those born in autumn, whatever their allergic predisposition.

Comparison between different age groups. To determine whether the effect of month of birth on the prevalence of AD can be seen from early childhood or from later childhood, the subjects were divided into 3 groups

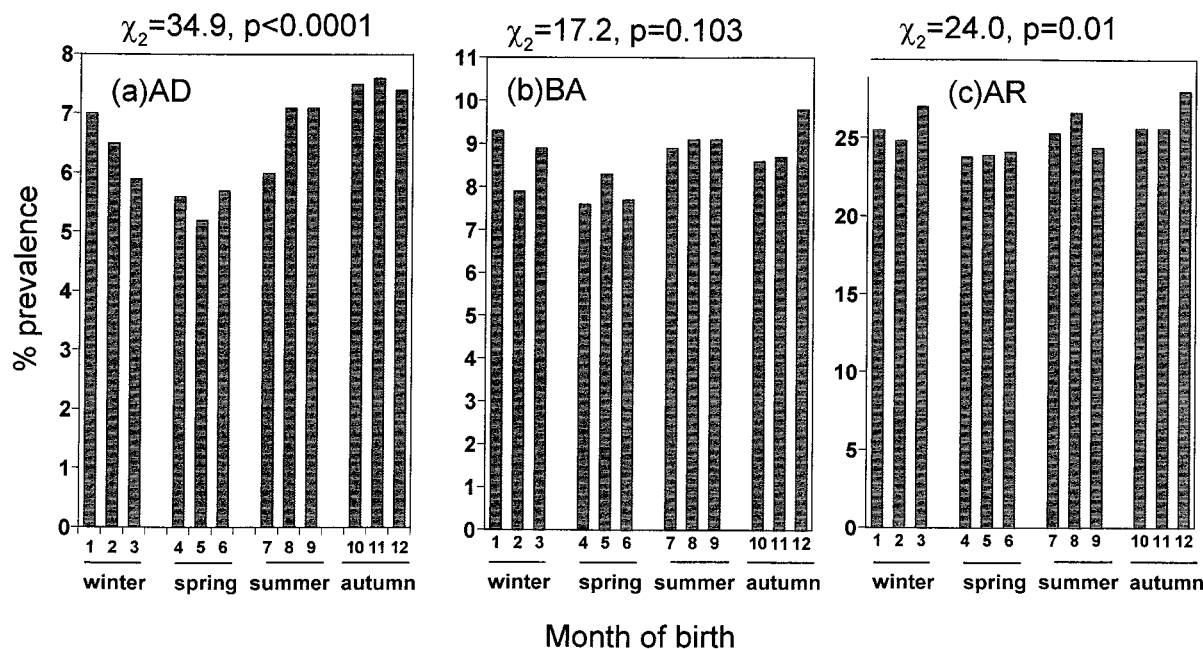


FIG 1. Month of birth and prevalence of allergic diseases in schoolchildren.

TABLE II. Logistic regression analysis for season of birth and prevalence of allergic diseases

Season of birth	AD		BA		AR	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Spring, Apr-June (n = 8401)	0.79 (0.71-0.88)	<.0001*	0.87 (0.68-1.11)	.261	0.95 (0.76-1.19)	.668
Summer, July-Sep (n = 8261)	1.04 (0.94-1.14)	.468	1.12 (0.90-1.39)	.325	1.04 (0.85-1.28)	.676
Autumn, Oct-Dec (n = 8955)	1.22 (1.01-1.34)	<.0001*	0.95 (0.76-1.18)	.651	0.93 (0.76-1.13)	.457
Winter, Jan-Mar (n = 8108)	0.97 (0.88-1.08)	.609	1.06 (0.84-1.34)	.602	1.09 (0.88-1.34)	.447

*Statistically significant.

TABLE III. Logistic regression analysis for season of birth and prevalence of AD: Comparison of different age groups

Season of birth	7 to 9 y (n = 10,855)		10 to 12 y (n = 11,849)		13 to 15 y (n = 11,021)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Spring (Apr-Jun)	0.81 (0.68-0.97)	.021*	0.75 (0.64-0.90)	.001*	0.81 (0.65-0.99)	.042*
Summer (Jul-Sep)	1.06 (0.90-1.25)	.476	1.01 (0.86-1.18)	.930	1.05 (0.87-1.27)	.600
Autumn (Oct-Dec)	1.14 (0.97-1.34)	.105	1.25 (1.07-1.46)	.040*	1.28 (1.06-1.54)	.011*
Winter (Jan-Mar)	1.00 (0.84-1.18)	.956	1.02 (0.87-1.20)	.803	0.89 (0.73-1.09)	.278

*Statistically significant.

according to age (7 to 9, 10 to 12, and 13 to 15 years) for a comparison of the relationship between month of birth and prevalence of AD. There was still a significant difference in this relationship for subjects aged 10 to 12 years ($\chi^2 = 22.6$, $P = .02$) and those aged 13 to 15 years ($\chi^2 = 21.0$, $P = .03$) (Fig 2). However, the difference was not statistically significant for subjects aged 7 to 9 years ($\chi^2 = 10.8$, $P = .456$), although there was still the same tendency, and the prevalence of AD in those born in May was significantly lower (OR: 0.744, CI: 0.555-0.996, $P = .047$).

Logistic regression analysis was performed for these age groups. Those born in spring showed a significantly lower prevalence of AD for all 3 groups, whereas those

born in autumn showed a significantly higher prevalence of AD for only age groups 10 to 12 and 13 to 15 years (Table III).

Water-holding capacity of uninvolved skin in children with AD

Although the reasons for the major differences in the prevalence of AD according to month of birth are not clear, we speculate that the higher prevalence of AD in autumn and the lower prevalence in spring might be related to skin conditions in early infancy. Those born in autumn spend the first several months in cold, dry weather, which leads to dry skin, whereas those born in spring spend the first several months in warm, humid weather,

TABLE IV. Water-holding capacity of uninvolved skin (conductance $\mu\Omega$)

	Forearm	Abdomen	Back
Subjects with AD (n = 72)	39.5 (20.0-72.3)*	15.0 (11.0-20.0)†	27.0 (15.5-40.5)†
Control subjects (n = 64)	54.0 (34.0-106.0)	36.0 (24.0-49.5)	53.0 (31.0-78.0)

Data is expressed as median (interquartile range).

* $P = .0042$.

† $P < .0001$

which results in moist skin. These differences in skin conditions in the first few months of life might be one of the factors that affect the prevalence of AD at school age. If dry skin is an etiologic factor in AD, it can be expected that apparently normal skin in children with AD is actually drier than that found in normal children. This speculation was supported by a separate study in which we compared the water-holding capacity of uninvolved skin in children with and without AD. A significantly lower capacity was observed in children with AD (Table IV), with the abdominal skin showing the most significant difference ($P < .0001$). In the meantime no statistically significant difference was observed for the water-holding capacity of abdominal skin among different age groups of children with AD (data not shown). These data indicate that children with AD tend to have dry skin even from early infancy. The difference in the water-holding capacity between the AD and control groups was not due to the difference in mean age (3.2 vs 5.7 years) because there was no statistical difference in water-holding capacity according to age, either in the AD or control groups (data not shown).

DISCUSSION

This is the first report to examine the prevalence of AD in a large-scale general population of young schoolchildren according to the month of birth. A significant relationship was found between the prevalence of AD in schoolchildren and the month of birth. Overall, AD is seen significantly less frequently in those born in spring, whereas it is significantly more common in those born in autumn. The same tendency was observed for AR, but with much less significance than for AD, whereas there was no such tendency in the case of BA. Although about 30% of the recovered samples were without date of birth and therefore were omitted from the analysis, we do not think this omission affected the results because there is no statistical difference in either age distribution or the prevalence of any allergic disease between subjects with and without date of birth. When children were divided into 3 groups according to age (7 to 9, 10 to 12, and 13 to 15 years), the same statistically significant deviation was observed in age groups 10 to 12 and 13 to 15 years but not in age group 7 to 9 years, although there was the same tendency. It has been shown in a whole population study of 1218 subjects on the Isle of Wight, that more 4-year-

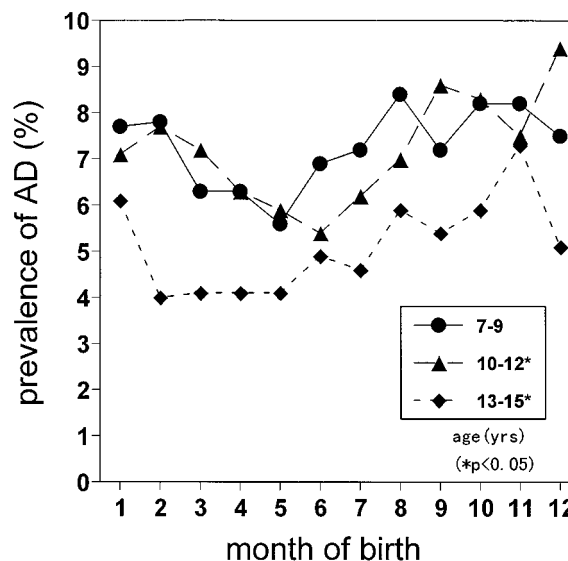


FIG 2. Month of birth and prevalence of AD: Comparison of different age groups.

old children born during autumn and winter had eczema compared with those born in spring and summer¹⁴ but that no such difference was observed among 2-year-old children.¹⁵ This data, combined with our findings, suggest that the effect of month of birth on prevalence of AD can be seen more clearly as children become older.

The key question is, of course, why AD is more prevalent in children born in autumn and less so in those born in spring. The same deviation is observed in AD with low allergic predisposition, suggesting that the seasonal variation is related to some unknown factors that are specific for AD but are not linked to allergic predisposition. Recently, dry skin and subsequent skin barrier disruption has attracted attention as a nonallergic etiologic factor of AD.^{16,17} Production of various inflammatory cytokines has been demonstrated at the barrier-disrupted skin of both mice^{18,19} and humans.²⁰ In addition, the antigen-presenting ability of skin Langerhans cells has been shown to increase after barrier disruption.²¹ Keratinocytes from atopic skin have been shown to overproduce GM-CSF and other cytokines both spontaneously²² and after stimulation with IFN- γ .²³ Thus it is possible that dry skin and subsequent barrier disruption lead to an immunologic dysregulation that may produce suitable conditions for allergens to be sensitized epicutaneously and to induce allergic inflammation on the skin. Tupker et al²⁴ have identified increased irritant susceptibility in both AD skin and control skin in winter, probably because of reduced barrier function, reduced skin hydration, and/or absence of the beneficial effect of ultraviolet light on cellular targets beneath the stratum corneum. On the basis of this evidence, we speculate that the higher prevalence of AD in those born in autumn and the lower prevalence in those born in spring might be related to skin conditions in early infancy. Those born in autumn spend the first several months in cold, dry weather, which

leads to dry skin, whereas those born in spring spend the first several months in warm, humid weather, which results in moist skin. These differences in skin conditions in the first few months of life might be one of the factors that trigger and/or aggravate allergic skin inflammation and ultimately affect the prevalence of AD at school age. In relation to this hypothesis, our study showed that not only the involved but also the uninvolved skin of children with AD tends to have a lower water-holding capacity. This tendency was observed in both older children and younger children under the age of 12 months. This data suggests that children with dry skin, whether inherent or environmentally induced, tend to have AD more frequently. This is in agreement with our hypothesis based on the etiologic survey.

It has been reported that repeated application of hapten to mouse skin induces a shift from an initial delayed-type hypersensitivity to an immediate-type reaction.^{25,26} It has also been shown that long-term topical application of ovalbumin results in a rise in total and ovalbumin-specific serum IgE and leads to localized allergic dermatitis.²⁷ Layers of the stratum corneum, which is responsible for skin barrier function, are thinner in early infancy. Combined with the fact that children born in autumn spend the first several months of their life mainly at home under skin drying conditions, this may lead to long-term epicutaneous exposure to and sensitization of indoor allergens and subsequent skin inflammation. This phenomenon should be more obvious in children who have an allergic predisposition and already have AD caused by food allergens. Once skin allergic inflammation is triggered, subsequent scratching, *Staphylococcus aureus* infection, and various nonspecific irritating stimuli may aggravate the inflammation and ultimately lead to long-term aggravation of the disease. If this is the case, appropriate skin care from early infancy to both prevent skin barrier disruption and block exposure to allergens that may penetrate the skin might reduce the prevalence of AD. In this respect, mite-blocking bedding encasing made from microfine fibers has been shown to be effective for preventing atopic infants from becoming sensitized to house dust mites.²⁸

In conclusion, we have shown that the month of birth affects the prevalence of AD among school-age children. We have also shown that patients with AD tend to have dry skin from early infancy. On the basis of these results, we speculate that the climate in early infancy affects skin condition and may ultimately affect the prevalence of AD. This might constitute at least one of the "nonallergic" etiologic factors of this complex disease.

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