

Change in prevalence of atopic dermatitis between 1986 and 2001 among children

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ABSTRACT

The prevalence of atopic dermatitis (AD) has increased during the last decades. Whether the prevalence is still increasing or has reached a stable level during the 1990s is still not certain. The purpose of this study was to compare the prevalence of AD in two different random samples of Danish children studied in 1986 and 2001 and to examine the associations between AD and other atopic outcomes. Two samples of children and adolescents living in urban Copenhagen were drawn at random from the civil registration list in 1986 and 2001. A total of 527 and 480 subjects participated in 1986 and 2001, respectively. Subjects were classified as AD cases when responding affirmatively to the question "Do you have, or have you ever had, significant and recurrent episodes of eczema in the folds of your elbows or knees?" Immunoglobulin E (IgE) measurements, skin-prick tests, and airway responsiveness tests were performed. The prevalence of AD increased from 17.3% in 1986 to 27.3% in 2001. For male subjects, the prevalence of AD was 16.4% in 1986 compared with 25.7% in 2001. For female subjects, the prevalence of AD was 18.1% in 1986 compared with 28.7% in 2001. Elevated levels of IgE, airway hyperresponsiveness (AHR), and rhinitis were statistically significant predictors of AD. The prevalence of AD has increased significantly from 1986 to 2001 in urban Copenhagen, Denmark. In addition, we found that AD was significantly associated with AHR, rhinitis, and elevated levels of IgE, supporting the idea of the atopic triad.

(Allergy Asthma Proc 29:392–396, 2008; doi: 10.2500/aap.2008.29.3139)

Key words: Airway hyperresponsiveness, atopic dermatitis, atopic triad, children, epidemiology, follow-up study, IgE, prevalence, rhinitis, skin test

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by a symmetric eczema, pruritus, lichenification, and excoriation of the face, neck, and flexural surfaces of the elbows and knees.^{1,2} Onset within the 1st years of living is typical, but a considerable portion of cases appears throughout childhood and early adulthood. AD is a complex disorder and is part of the atopic triad that also includes allergic rhinitis and asthma.³ High levels of immunoglobulin E (IgE) often accompany AD, suggesting that patients with AD have an underlying tendency to be sensitized to various allergens. This is consistent with the high occurrence of allergic disorders among this group of patients. The course of the disorder varies, and the severity and morphological pattern of the condition differs significantly between subjects. The clinical spectrum ranges from minor forms presented by a few dry eczematous patches to major forms with large areas of erythematous rash.

There is no golden standard for diagnosing AD although several criteria have been proposed.^{4,5}

The prevalence of AD has been discussed in many studies during the last decades. It is generally acknowledged that there has been a substantial increase since the 1960s,⁶ but this increase in prevalence varies considerably among different geographic regions.⁷ In Denmark, Schultz Larsen reported a threefold increase from 3% in the 1960s to 10% in the 1970s in a population-based twin sample.⁷ Moreover, a study by Olesen *et al.* found a cumulative incidence of 18.9% in 1993 compared with 19.6% in 1998,⁸ and concluded that the increase was now stable. Mortz *et al.* conducted an epidemiologic follow-up study in the municipality of Odense, Denmark, that concluded that the lifetime prevalence of AD had increased to 21.3% in 1995.⁹

The reasons for the increase in the prevalence of AD during the last decades are not known but studies have shown that the increase is seen especially in countries with a western lifestyle.^{6,7} Another consideration is whether the increase in prevalence of AD is because of an actual increase in incidence or to a prolonged activity in AD.⁸ This clinical follow-up study aimed to compare the prevalence of AD in two different random samples of Danish children, 7–17 years of age, studied in 1986 and 2001, and, second-

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Sponsored by a grant from the Copenhagen Hospital Corporation

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arily, to examine the associations between AD and other atopic outcomes.

METHODS

Subjects

Two random samples of children and adolescents living in urban Copenhagen, Denmark, were studied. The first sample was examined in 1986 and the second was studied in 2001.¹⁰ All subjects were drawn at random from the civil registration list. The mean age was 12 years (age range, 7–17 years). In 1986 and 2001, a total of 1000 and 1500 subjects, respectively, were identified. Because of incorrect information on postal addresses, only 983 and 1440 in 1986 and 2001, respectively, were eligible for participation. By letter, these subjects were invited to participate in the studies. In 1986, a total of 527 (53.6%) participated, whereas in 2001, a total of 480 (33.3%) participated.

To ensure the robustness of the study, telephone interviews were conducted with 100 and 116 randomly selected subjects from the group of nonrespondents in 1986 and 2001, respectively. The interviews were conducted with the same questionnaire that was used in the clinical setting. For every household the interview was conducted with the child, and, subsequently, a parent was consulted to confirm the obtained information. The 100 and 116 subjects in 1986 and 2001, respectively, did not differ significantly from the subjects originally included with respect to sex, age, and disposition to atopy. In 2001 the prevalence of AD was not different in the group interviewed by telephone compared with the clinically studied subjects; this information was unavailable in 1986. The children interviewed by telephone were not included in the final analysis since objective measurements were not obtained from these subjects.

Clinical Interview

A physician interviewed all studied subjects. AD was diagnosed with the question: “Do you have, or have you ever had, significant recurrent episodes of eczema in the folds of your elbows or knees?” Information on wheezy bronchitis and birth weight was based on parental reporting. Parental atopic disease was defined as symptoms of hay fever and/or asthma in at least one parent when exposed to allergens encountered in the standard testing panel described later. This method is comparable with the one used in the European Community Respiratory Health Survey.¹¹ Symptoms among participants were assessed with the same set of questions used to detect parental affectedness. These were “Have you ever had hay fever?” “Have you ever had episodes of runny or stuffy nose or sneezing when not having a cold?” “Have you ever had asthma?” and “Have you ever had episodes of wheezing with short-

ness of breath?” This information was obtained on the day of examination by interview with a physician. Consensus was reached with the accompanying parent. Rhinitis and asthma were defined as being present when a positive answer was provided to either and at least one of the two questions on hay fever or the two questions on asthma, respectively.

Skin-Prick Test (SPT) and Measurements of Serum Total IgE

SPTs were performed using standard dilutions of nine common aeroallergens. The allergens used were birch, grass, mugwort, horse, dog, cat, house-dust mite (*Dermatophagoides pteronyssinus*), and mold (*Alternaria iridis* and *Cladosporium herbarium*) with positive and negative references being histamine, 10 mg/mL, in 50% glycerol and glycerol, 50%, respectively. The concentrations of allergens were 100.000 BU/mL (Phazet system; Pharmacia, Copenhagen, Denmark) in 1986 and 10 HEP (histamine equivalent prick; Soluprick SQ system; ALK Abelló, Denmark) in 2001. A comparison of the two tests has shown that the frequency of positive reactions to the majority of the allergens was similar and that the frequency of reactions of 3 mm or more differed only slightly.¹² Reactions were read after 15 minutes. A positive result was defined as a positive reaction to at least one of the allergens, and a reaction was considered positive if the mean wheal diameter was at least 3 mm.¹³ The participants were requested to discontinue medications that contained antihistamines at least 3 days before skin testing.

Levels of serum total IgE were measured with a paper radioimmunosorbent test (PRIST; Pharmacia) in 1986 and with an enzyme-linked immunosorbent assay (ELISA, on Immulite 2500; DPC, Tarrytown, NY) in 2001. Results were expressed in kilo international units per liter. Serum total IgE was considered elevated when above 150 kIU/L.

Airway Responsiveness Tests

The methods by Cockcroft and Yan were used for measuring airway responsiveness to inhaled histamine in 1986 and 2001, respectively.^{14,15} According to the Cockcroft method, a Wright nebulizer delivered the histamine and the subjects inhaled by normal tidal volume breathing. Nine concentrations of histamine were used, from 0 (saline) to 8 mg/mL and the test was terminated when the maximum concentration was reached or when a drop in forced expiratory volume in 1 second (FEV₁) of more than 20% was observed—the provocative concentration (PC₂₀). Airway hyperresponsiveness (AHR) was defined as a PC₂₀ of 8 mg/mL. According to the method by Yan, each aerosol was inhaled starting with saline and followed by increasing doses of histamine until a cumulative dose of 7.8 μ mol

Table 1 Characteristics of subjects with and without a history of atopic dermatitis in Danish children who are 7–17 years of age

Variable	Affected (n = 222)	Unaffected (n = 785)	p Value
Demographics			
Female sex (%)	55.0	51.1	0.308
Age (mean)	12.0	12.2	0.342
Body mass index (mean)	18.9	18.9	0.890
Birth weight (mean, kg/10)	33.8	34.0	0.770
Parental atopic disease (%)	46.4	36.5	0.007
Objective tests			
AHR (%)	18.2	9.7	0.001
FEV ₁ /FVC (mean, %)	89.3	89.5	0.671
Positive skin prick test (%)	31.7	19.1	0.00007
Birch (%)*	36.2	21.8	0.025
Grass (%)*	40.6	32.7	0.255
Mugwort (%)*	18.8	16.3	0.647
Horse (%)*	20.3	15.0	0.328
Dog (%)*	42.0	21.8	0.002
Cat (%)*	46.4	21.8	0.0002
HDM allergen (%)*	49.3	56.5	0.323
<i>Alternaria</i> (%)*	5.8	7.5	0.779
<i>Cladosporium</i> (%)*	5.8	1.4	0.084
≥2 Sensitizations (%)	65.2	44.8	0.005
Elevated serum total IgE (%)	27.0	15.4	0.0002
Concurrent disorders			
Wheezy bronchitis (%)	16.2	9.9	0.009
Asthma (%)	11.7	5.9	0.003
Rhinitis (%)	40.1	22.5	0.0000001

*Percentage of subjects with a positive reaction to the particular allergen among subjects who are sensitized.

AHR = airway hyperresponsiveness; FVC = forced vital capacity; HDM = house-dust mite; SPT = skin-prick test.

had been reached. The test was terminated when the maximum concentration had been reached or when a 20% decline in FEV₁ had occurred before the end of the dosing regimen. For all subjects experiencing at least a 20% decline in FEV₁ the concentration causing a 20% fall in FEV₁ (PD₂₀) was calculated. A positive test result (AHR) was defined as a PD₂₀ below 3.9 μmol. The degree of airway obstruction was calculated as FEV₁ divided by the forced vital capacity.

Statistical Analysis

The prevalence of AD in 1986 was compared with 2001 using a chi-square test. Logistic regression with backward elimination was performed to examine the effects of explanatory variables on the risk of AD. Year of examination, age, sex, birth weight, wheezy bronchitis, parental atopic disease, degree of airway obstruction, asthma, rhinitis, AHR, positive SPT, and elevated serum total IgE were explanatory variables. Subjects with incomplete data on any of the explanatory variables were excluded from the analysis. The results are reported as odds ratios (ORs). A value of

$p < 0.05$ was considered statistically significant. Data were analyzed with the statistical package SPSS 16.0 (SPSS, Inc., Chicago, IL). The Scientific Ethics Committee approved the study and informed consent was obtained from all participating subjects and their parents.

RESULTS

We observed no significant differences in sex (50.3% versus 53.8%, female subjects; $p = 0.27$), age (12.2 years versus 12.2 years; $p = 0.84$), or body mass index (18.2 kg/m² versus 19.0 kg/m²; $p = 0.36$) between the cohorts from 1986 and 2001. Additional characteristics of the study subjects are given in Table 1. Children with a history of AD differed from children without a history of AD with respect to familial predisposition to atopic disease, occurrence of AHR, positive SPT, elevated serum total IgE, wheezy bronchitis, asthma, and rhinitis. Analysis of individual sensitization patterns among subjects with a positive SPT showed that subjects with a history of AD were more likely to be sensitized toward indoor allergens such as dogs and cats.

Table 2 Factors that significantly predict a history of atopic dermatitis in Danish children who are 7–17 years of age

	+AD (%)	–AD (%)	OR (95% CI)	<i>p</i> Value
Year			1.63 (1.16–2.27)	0.005
1986	91 (17.3)	436 (82.7)		
2001	131 (27.3)	349 (72.7)		
Total IgE*	55 (27.0)	112 (15.4)	1.51 (1.01–2.27)	0.046
AHR#	38 (18.2)	74 (9.7)	1.81 (1.13–2.89)	0.014
Rhinitis§	89 (40.1)	177 (22.5)	1.91 (1.33–2.75)	<0.001

Results are adjusted for, age, sex, birth weight, wheezy bronchitis, parental atopic disease, degree of airway obstruction, positive skin-prick test, and asthma.

*Number of subjects with serum total IgE above 150 kIU/L.

#Number of subjects with airway hyperresponsiveness.

§Number of subjects with rhinitis.

±AD = subjects with and without a history of atopic dermatitis; AHR = airway hyperresponsiveness.

The prevalence of AD increased from 17.3% in 1986 to 27.3% in 2001 (OR = 1.80; 95% CI [1.33–2.43], $p < 0.001$). For male subjects, the prevalence of AD was 16.4% in 1986 compared with 25.7% in 2001 (OR = 1.80; 95% CI [1.13–2.74]; $p = 0.01$), whereas for female subjects it was 18.1% in 1986 compared with 28.7% in 2001 (OR = 1.82; 95% CI [1.20–2.75]; $p = 0.004$). The results remained statistically significant when adjusting for age, sex, birth weight, wheezy bronchitis, parental atopic disease, degree of airway obstruction, asthma, rhinitis, AHR, positive SPT, and elevated serum total IgE (Table 2).

DISCUSSION

This study showed an increase in the prevalence of AD from 17.3% in 1986 to 27.3% in 2001. Our analysis suggested that the increase was almost equal among male and female subjects, however, with a higher overall prevalence among female subjects. In addition, we found that children with a history of AD more often have AHR, rhinitis, and higher levels of serum total IgE than the background population, consistent with the general idea of the atopic triad composed of rhinitis, asthma, and dermatitis.

There has been a substantial increase in the prevalence of AD since the 1960s,⁶ but one other study from Denmark by Olesen *et al.* compared the cumulative incidence from 1993 and 1998 and concluded that the increase was stable at a level of 19.6% in 1998.⁸ Our study showed a prevalence of 27% in 2001, which indicates that the level of AD could still be increasing. We were not able to determine at what point in time or at what rate the increase in prevalence had taken place. However, our results are consistent with a study by Grize *et al.* of Swiss children in the age group of 5–7 years who were investigated every 3rd year with respect to AD and other atopic diseases. Their results

showed a significant increase in the prevalence of AD from 1992 to 2001, primarily among girls.¹⁶ A study by Broberg and colleagues examined the cumulative incidence and point prevalence of AD within Swedish school children aged 5–6 years in the period from 1992 to 1998.¹⁷ Their results showed that the prevalence of AD had increased over time. These results concur with our results and contradict the conclusion that the prevalence of AD is now stable. On the contrary, a Norwegian questionnaire-based study by Selnes *et al.* showed that the prevalence of AD had increased substantially between 1985 and 1995 but did not change from 1995 to 2000,¹⁸ reflecting large geographical variation in AD prevalence, both between and within countries.¹⁹ The results from these investigations suggest that environmental factors that vary between countries and from urban to rural life may be critical to the development of atopic disorders in childhood. Environmental factors associated with a western lifestyle seem to be of great importance for developing atopic diseases.²⁰ In particular, McNally and colleagues observed a higher risk of AD in four urban regions in the United Kingdom, emphasizing the importance of climatic factors, hard water, air pollution, and exhaust pollution as important environmental risk factors.²¹ A parallel can be drawn to the diverging prevalence in our study in urban Copenhagen compared with the study by Olesen *et al.* in rural Denmark. Still, other risk factors may also be important such as intrauterine and infant environment, changes in maternal diet, reduced infant infections, and increased use of antibiotics.⁸ There is also a strong relationship between AD and socioeconomic advantage (as measured by occupation of parents or household tenure) and small family size,² which are trends that are still more and more pronounced in urban Copenhagen. McNally *et al.* explored the relation between home environment and AD in

Nottingham, U.K., and found a statistically significant association between AD and dampness in the home, the use of a radiator to heat the child's bedroom, and the use of synthetic pillows.²² They also found that frequent vacuuming in the home was associated with a decreased prevalence of AD consistent with a possible role of indoor allergens in the etiology of AD. Our observation of an increased risk of sensitization toward dogs and cats among subjects with AD supports this idea.

We diagnosed AD with the question, "Do you have or have you ever had, significant and recurrent episodes of eczema in the folds of your elbows or knees?" and not with a series of questions according to recommended practice.⁷ Additional questions would likely have ensured the diagnosis and reduced the chance of over-/underreporting, as would a higher response rate in the clinical examination. Furthermore, we rest partly on parental and patients' recollections, which increases the chance of recall bias. The increased awareness of AD in the population could have influenced parents' attention toward symptoms of AD, particularly in the second cohort leading to inflated prevalence estimates. However, the prevalence of AD among nonrespondents (in 2001) was compatible with the individuals who were clinically examined (24.1% versus 27.3%) and therefore reassures that the change in prevalence of AD between 1986 and 2001 has not been overestimated.

In conclusion, we found an increase in the prevalence of AD from 1986 to 2001 in both sexes. In addition, we found that AD was significantly associated with AHR, rhinitis, and elevated levels of serum total IgE, supporting the idea of the atopic triad. Further exploration regarding the geographical variation between and within countries is necessary to determine whether the prevalence has reached a stable level or is still increasing.

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