

CLINICAL REPORT

Recall Bias in Childhood Atopic Diseases Among Adults in The Odense Adolescence Cohort Study

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Atopic dermatitis (AD) is a common disease in childhood and an important risk factor for the later development of other atopic diseases. Many publications on childhood AD use questionnaires based on information obtained in adulthood, which introduce the possibility of recall bias. In a prospective cohort study, recall bias was evaluated in 1,501 unselected schoolchildren (mean age 14 years) evaluated for the first time in 1995 with a standardized questionnaire combined with a clinical examination and repeated in 2010. The lifetime prevalence of AD was 34.1% including data obtained both during school age and 15 years later, compared with 23.6% including data only from adulthood. The most important factors for remembering having had AD in childhood were: (i) long duration of dermatitis in childhood; (ii) adult hand eczema; and (iii) concomitant atopic disease. Recall bias for childhood AD affected the results of logistic regression on adult hand eczema and is a significant problem in retrospective epidemiological questionnaire studies evaluating previous AD as a risk factor for development of other diseases. Key words: recall bias; atopic dermatitis; asthma; allergic rhinitis; questionnaire; prospective studies.

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Atopic dermatitis (AD) is common, with a lifetime prevalence in the general population of approximately 20–25% (1, 2). AD usually starts before the age of 2 years, and many children outgrow the disease before starting school (3, 4). AD is considered one of the most important risk factors for developing adult hand eczema (5, 6). Since most studies of hand eczema in adults are cross-sectional or have a follow-up period during adult life, these studies assess risk factors in childhood based on questionnaires performed in adulthood. Self-report questionnaires asking adults about risk factors in childhood have the drawbacks of recall bias and the possibility of misclassifying the diagnosis of AD. Even a short pas-

sage of time can introduce a major recall bias, as people forget that they have had eczema (7). When asking adults about diseases occurring before school age the answers would therefore be even less accurate.

The present study evaluated schoolchildren in the 8th grade (mean age 14 years) in 1995 using a standardized questionnaire answered by the children and their parents, combined with a clinical examination for eczema. The same procedure was repeated 15 years later in the same population (mean age 29 years, parents not involved) to evaluate the course of atopic diseases and recall bias.

MATERIAL AND METHODS

Population and study design

Phase One of The Odense Adolescence Cohort Study (TOACS) was conducted in 1995–96 as a cross-sectional study among 1,501 8th grade schoolchildren in the Municipality of Odense, encompassing questionnaires, interviews and clinical examinations, blood samples for immunoglobulin E (IgE) measurement and patch tests. Phase Two was conducted in 1996–97 as a case-control study in selected groups of schoolchildren (1).

Phase Three is a 15-year follow-up study in the same population (28–30 years of age). From the original cohort, 1,271 subjects had provided consent to be contacted again and had provided their personal identification number for tracing. An invitation to the follow-up study was sent in 2010 together with a code to access an online questionnaire with 147 questions. If subjects did not answer after having been sent 2 reminders, the questionnaire was sent twice more as a paper version. Furthermore, participants were offered a clinical examination, measurement of specific IgE, skin-prick tests, pulmonary function test and patch tests. The examination and testing was performed in Odense, Copenhagen and Aarhus by the same investigator (CGM) who performed the Phase One and Two studies, assisted by 2 experienced dermatological nurses and a laboratory technician. Details of the follow-up study are published elsewhere (5, 8, 9).

Phase Three questionnaire

The respondents completed the questionnaire with questions on AD, asthma, allergic rhino-conjunctivitis, hand eczema, urticaria/angioedema and Type I and IV allergy. The questionnaire included the same questions as in Phase One, supplemented with new questions that included occupational aspects. In Phase One the schoolchildren and their parents were asked to complete the questionnaire together, while the young adults completed the questionnaire by themselves in Phase Three.

The lifetime prevalence of AD was defined by published questionnaire criteria based on several questions (Schultz Lar-

sen criteria (2) with a sensitivity of 88% and a specificity of 89%. Furthermore, a single question on the lifetime prevalence of AD was included based on the Tuohilampi questionnaire: "Have you ever had childhood eczema (AD), an itchy rash (eczema) which has affected skin creases or folds (folds of elbows, behind the knees)?" (10, 11).

The lifetime prevalences of asthma and allergic rhinitis were evaluated using the Tuohilampi questionnaire/NOSQ-2002 questionnaire, by answering the 2 questions: "Have you ever had asthma?" and "Have you ever had 'hay fever' or other symptoms of nasal allergy (bouts of sneezing, itchy or running nose)" from e.g. pollen or animals?" (10, 11). A question on allergic eye symptoms was also included.

All questions on atopic diseases were followed by the question, "Was the diagnosis confirmed by a doctor?"

The lifetime prevalence of hand eczema was also determined by using the Tuohilampi questionnaire/NOSQ-2002 questionnaire (10, 11). The criteria for a history of hand eczema were eczema (rash) on the fingers, finger webs, palms or back of hands, which had appeared once and continued for at least 2 weeks, or had appeared several times, or had been persistent.

Clinical examination

The 1-year period prevalence and point prevalence of AD were evaluated clinically according to the Hanifin & Rajka criteria (12) both in 1995 and 2010 by a dermatologist (CGM).

Ethics

The study was approved by the Regional Ethical Committee for Southern Denmark (S-VF-19950022).

Data handling and statistics

A total of 743 of the respondents answered the electronic questionnaire, while 156 answered the paper version. The responses from the paper version were subsequently entered into the database by the first author (CGM). All data from the clinical examination were entered twice. When differences were found, a comparison with raw input forms was made and corrections made accordingly. Statistical analysis was performed with STATA/SE 11.0 (Stata Corporation, TX, USA).

The results are given as prevalence proportions and 95% confidence interval (CI). Comparisons were made using χ^2 -based table analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

A total of 1,206 subjects of the 1,271 (95%) from the original cohort were retrieved in Denmark through the national central person register; 4 had died, 1 person was missing, and 60 had emigrated. After 4 reminders the response rate for answering the questionnaire was 74.6% (899/1,206), and 469/1,206 (38.9%) of the invited subjects (52.2% of those who responded by questionnaire) participated in the clinical examination. The 899 subjects answering the questionnaire in 2010 were a representative part of the 1995 population, except that more women than men participated in the follow-up questionnaire and more with AD in childhood participated, as shown in Table I (5).

Table II shows the lifetime prevalence of AD (Schultz Larsen criteria [2]) in the cohort of persons participating

Table I. Comparison of baseline characteristics (1995) between participants and non-participants in the questionnaire in the follow-up study (2010) (reproduced from ref. 5)

Baseline characteristics 1995	Participants 2010 Prevalence, % (n)	Non-participants 2010 Prevalence, % (n)	p-value
Sex			
Female	56.3 (506)	38.4 (207)	<0.05
Male	43.7 (393)	61.6 (332)	
Present or past:			
Atopic dermatitis	23.9 (215/899)	16.9 (91/539)	<0.003
Hand eczema	9.8 (88/899)	8.4 (45/539)	0.36
Allergic rhinitis	19.7 (177/899)	16.9 (91/539)	0.19
Asthma	12.0 (108/899)	11.3 (61/539)	0.69
Present:			
Contact allergy ^a	15.4 (120/778)	14.7 (54/368)	0.74
Positive specific IgE ^b	28.1 (171/609)	33.1 (86/260)	0.14

^aIn Phase One 1,146 of the 1,438 participated in patch testing.

^bIn Phase One 869 of the 1,438 participated in blood sample for IgE measurement.

in both Phase One and Phase Three. The lifetime prevalence of AD was 24.0% in Phase One; 15 years later a similar lifetime prevalence was found (23.6%; 95% CI 20.9–26.6). However, on pooling those reporting AD in 1995 and/or 2010, the lifetime prevalence was 34.1% (95% CI 31.0–37.2).

In 1995, 215/897 fulfilled the criteria for AD. In 2010, however, only 121 of the original 215 subjects could identify themselves as having had childhood AD based on the same questions (Fig. 1), while 94 did not recall childhood AD (94/215; 43.7%, 95% CI 37.0–50.6). Among the 94 subjects not found in 2010, 56 had reported AD in 1995, with onset before the age of 5 years (34 before 2 years of age, and 22 between 2 and 5 years of age). In 30 of the 56 subjects, the dermatitis had cleared in less than 5 years. In 2010, 91 new cases were found (Fig. 1).

It was not possible to estimate a lifetime prevalence of AD based on clinical examination because the participants were only examined twice during the study period (1995 and 2010). According to the Hanifin &

Table II. Lifetime prevalence of atopic dermatitis (AD) (Schultz Larsen criteria (2)) in the 897 participating in both Phase One and Three questionnaires

	Total population n = 897 ^a % (n) [95% CI]	Women n = 505 % (n)	Men n = 392 % (n)
Ever AD			
Phase One and/or Three (lifetime 0–29 years)	34.1 (306) [31.1–37.3]	38.0 (192)	29.1 (114)
Ever AD			
Phase Three (lifetime 0–29 years)	23.6 (212) [20.9–26.6]	26.5 (134)	19.9 (78)
Ever AD			
Phase One (lifetime 0–14 years)	24.0 (215)	27.5 (139)	19.4 (76)

^aIn total 899 subjects answered the questionnaire; however, only 897 answered the questions on atopic dermatitis.

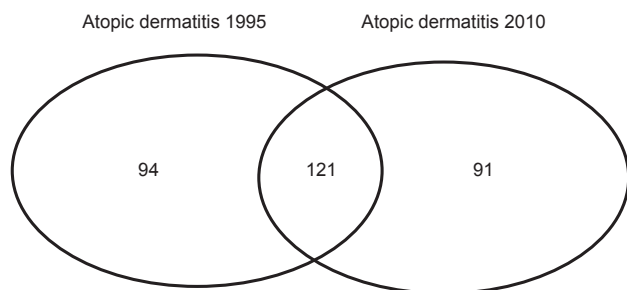


Fig. 1. Relationship between atopic dermatitis in 1995 and 2010. Number of persons reporting atopic dermatitis ever in 1995 and when asked the same questionnaire again after 15 years in 2010. In total 215 reported atopic dermatitis by questionnaire in 1995. Of these, 121 answered the same in 2010 while 94 did not recall atopic dermatitis in childhood when asked again 15 years later. In 2010, 91 new cases were found.

Rajka criteria (12), the 1-year period prevalence of AD in 1995 was 6.7% (90/1,340) and the point prevalence 3.6% (48/1340). In 2010 the 1-year period prevalence was 10.0% (47/469) and the point prevalence 6.2% (29/469). In 2010, 36/47 subjects with AD during the last year also had hand eczema (adults fulfilling the Hanifin & Rajka criteria for AD and having eczema on

Table III. Lifetime prevalence of atopic dermatitis (AD), allergic rhinitis (AR) and asthma based on single questions (Tuohilampi questionnaire (10, 11)) in the 897 participating in both Phase One and Three questionnaires

	Total population <i>n</i> = 897 ^a % (<i>n</i>) [95% CI]	Women <i>n</i> = 505 % (<i>n</i>)	Men <i>n</i> = 392 % (<i>n</i>)
<i>Ever AD</i>			
Phase One and/or Three (lifetime 0–29 years)	28.2 (253) [25.3–31.3]	31.5 (159)	24.0 (94)
<i>Ever AD</i>			
Phase Three (lifetime 0–29 years)	18.8 (169) [16.3–21.6]	22.0 (111)	14.8 (58)
<i>Ever AD</i>			
Phase One (lifetime 0–14 years)	21.6 (194)	23.8 (120)	18.9 (74)
<i>Ever AR</i>			
Phase One and/or Three (lifetime 0–29 years)	40.8 (366) [37.6–44.1]	41.4 (209)	40.1 (157)
<i>Ever AR</i>			
Phase Three (lifetime 0–29 years)	36.2 (325) [33.1–39.5]	35.8 (181)	36.7 (144)
<i>Ever AR</i>			
Phase One (lifetime 0–14 years)	19.7 (177)	20.2 (102)	19.1 (75)
<i>Ever asthma</i>			
Phase One and/or Three (lifetime 0–29 years)	20.2 (181) [17.6–23.0]	22.2 (112)	17.6 (69)
<i>Ever asthma</i>			
Phase Three (lifetime 0–29 years)	17.3 (155) [14.9–19.9]	18.8 (95)	15.3 (60)
<i>Ever asthma</i>			
Phase One (lifetime 0–14 years)	12.0 (108)	10.9 (55)	13.5 (53)

^aIn total 899 subjects answered the questionnaire; however, only 897 answered the questions on atopic dermatitis, asthma and allergic rhinitis.

their hands). On the other hand, in 2010, 81/127 subjects with hand eczema during the last year had or had had AD. The association between AD and hand eczema, including different types of hand eczema, has been described previously (5). Almost all patients diagnosed as having AD (Hanifin & Rajka) by the dermatologist during the clinical examination were also identified by the questionnaire criteria (Schultz Larsen criteria) both in 1995 (85/90) and in 2010 (44/47).

Using a single question on AD (Tuohilampi questionnaire) both in 1995 and 2010 a similar result was obtained (Table III) as using the published questionnaire criteria from Schultz Larsen (Table II). In 1995, 21.6% of subjects answered that they have/have had AD; in 2010 this proportion had reduced to 18.8%. However, by pooling the data from 1995 and 2010, lifetime prevalence increased to 28.2% (95% CI 25.3–31.3) instead of 18.8% (95% CI 16.3–21.6). In 1995, 194/897 answered “yes” to AD, and in 2010 only 110 of the 194 gave the same answer. Fifty of the 84 subjects giving a negative answer in 2010 had their debut of AD before the age of 5 years (34 before the age of 2 years, 16 between the age of 2 and 5 years), and 32/50 had a duration of AD of less than 5 years.

Compared with AD, the lifetime prevalence of asthma and allergic rhinitis was nearly identical, as evaluated by the questionnaire in 2010 compared with results evaluated by pooled data from 1995 and 2010 (Table III).

The same questions on hand eczema were also used both in 1995 and 2010. The lifetime prevalence calculated by pooling the data from 1995 and 2010 was 23.0% (95% CI 20.3–25.9) compared with 18.2% (95% CI 15.7–20.9) using data reported only in 2010 (data not shown). Hand eczema was found in 42.8% of subjects with AD.

When examining different factors (Table IV) in those subjects fulfilling the criteria for AD in both 1995 and 2010 (Schultz Larsen criteria) compared with those not recalling AD in childhood, the most important factors for remembering AD were: (i) long duration of dermatitis in childhood; (ii) adult hand eczema; and (iii) concomitant atopic diseases. Middle to high educational level compared with no or short education did not affect recall.

Of the 306 fulfilling the Schultz Larsen criteria for AD ever (1995 and/or 2010) 153 reported dermatitis during the last year in 2010 (50%), while 50% had outgrown the dermatitis.

In the 153 with present AD, 45 reported a duration of AD of more than 20 years, 39 of 10–20 years, 30 of 5–10 years, and 38 of less than 5 years (1 did not know).

Looking at those with present AD and duration less than 10 years, it appears that 68/306 of subjects should have developed AD after the age of 18 years. However, including data from 1995, 29/68 already fulfilled the criteria for AD in adolescence. This means that no more

Table IV. Different factors in relation to the group of adults remembering having had atopic dermatitis (AD) in childhood compared with those not recalling AD in childhood (Schultz Larsen criteria (2))

	Remembering AD in childhood % (n)	Do not recall AD in childhood % (n)	p-value
Duration of AD > 10 years at 14 years of age	54.5 (66/121)	21.3 (20/94)	<0.001
Hand eczema during the last year as adult ^a	40.0 (48/120)	5.4 (5/93)	<0.001
Visit to a physician due to hand eczema as adult ^a	23.3 (28/120)	1.2 (1/93)	<0.001
Allergic rhinitis	64.5 (78/121)	42.6 (40/94)	<0.003
Asthma	38.8 (47/121)	21.3 (20/94)	<0.03
Middle–high educational level	52.9 (64/121)	52.1 (49/94)	NS

^aTwo did not answer the questions on hand eczema in 2010.

NS: not significant.

than 39/306 (12.7%) with AD could have developed AD after the age of 18 years.

DISCUSSION

Recall bias is a major problem in retrospective epidemiological studies in adults, especially when including information about diseases in childhood. We found that a significant proportion of adults forgot that they had had childhood AD when they responded to a questionnaire at the age of 29 years compared with the answer given by themselves and their parents 15 years earlier. Those who remembered AD with a 15-year interval more often had a long duration of AD in childhood, hand eczema in adulthood and other atopic diseases. A study from Wisconsin showed that even a short passage of time can introduce major recall bias (7): in adults with AD, only 59% self-reported the disease correctly, and even parental recall of skin disease in children was only 70%. Furthermore, a Swedish study reported that 29% of subjects diagnosed with AD in the school health medical records could not recall that they had had the disease when asked 20–30 years later (13). Those remembering having AD in childhood had a higher prevalence of dermatitis after the age of 15 years and a higher prevalence of hand eczema, in agreement with our results. Cultural and educational factors may also affect the response to questionnaires on AD (14). However, educational level did not affect recall bias in this study. The severity of AD in childhood was not evaluated in the questionnaire and therefore not included in the analysis. It is possible that those with severe AD in childhood tend to remember having had AD in childhood compared with those with only mild dermatitis. Furthermore, in childhood the questionnaire was answered by the parent and the schoolchildren, while the questionnaire 15 years later was answered only by the young adults. This can affect recall, as parents remember diseases from early childhood that the 29-year-old adults did not recall.

Compared with the results obtained for AD, patients tend to have less recall bias regarding asthma and allergic rhinitis, perhaps due to the later debut of these

diseases (in older childhood and adolescence). Furthermore, the occurrence of repeated attacks of asthma or rhinitis may increase memory and limit recall bias.

In the TOACS cohort, 50% of the adults with AD had outgrown their eczema in 2010, and those with persistent AD as adults often had a long duration of AD. Less than 13% of those with adult AD had been first diagnosed after 18 years of age.

A questionnaire-based study always carries the risk of misclassification of diseases compared with the clinical diagnosis, which must be considered “the true diagnosis”. Much effort has been made to make validated questionnaires for the diagnosis AD (2, 15, 16). However, it can be difficult to make a questionnaire feasible for all age groups, e.g. infants, children, adolescents and adults. At the time of this study in 1994–95, the only validated questionnaire in Danish was chosen for evaluation of AD (2). The same questionnaire was used 15 years later, knowing that the questionnaire had not been validated in adults. Nearly all patients with a clinical diagnosis of AD present at the age of 14 years and 29 years were found by the questionnaire. As we did not perform periodic clinical examination of the cohort, the lifetime prevalence of AD cannot be estimated by clinical examination, and we are unable to determine if the questionnaire overestimated the prevalence of AD. In 1995 and 2010 a single question on AD was used in another part of the questionnaire, together with questions on asthma and allergic rhinitis, which gave a nearly identical estimation of AD as the questionnaire-based criteria based on summation of 18 questions (Schultz Larsen criteria). In a recent study from Sweden it was shown that the answer to a single question on AD tends to overestimate the prevalence of AD (17). In the Swedish study, 71% of cases with AD identified in the school health medical system answered “yes” to having had AD (29% answered “no”), while 10% of controls answered “yes” to having had AD. The specificity was 71% and the sensitivity 90%. The sensitivity was higher and the specificity was lower in a subgroup with current hand eczema. Patients without AD sometimes report childhood AD because they have had some eczema or other skin diseases that are misclassified as AD (e.g.

allergic contact dermatitis, irritant contact dermatitis, seborrhoeic dermatitis or skin diseases such as psoriasis or fungal infection).

We found that a large proportion of young adults did not recall AD in childhood, either using a validated questionnaire with 18 questions on AD or a single question on AD. They did, however, recall asthma and allergic rhinitis. Studies on hand eczema in adults, often include questions on childhood AD when evaluating risk factors for adult hand eczema, and the magnitude of recall bias will influence the analysis for risk factors in such studies. In prospective follow-up studies risk factors from childhood can be evaluated in relation to the development of adult disease. However, if the study is retrospective, recall bias regarding factors from childhood can be presented and can affect risk assessment. Earlier we reported risk factors for adult hand eczema (5). We showed that childhood AD (AD diagnosed in 1995) is a risk factor for adult hand eczema in a logistic regression model with an odds ratio (OR) of 1.9 (5) (prospective follow-up study). However, if we used data on childhood AD obtained in 2010 (retrospective design) in the same logistic regression model an OR of 4.1 was obtained (data not shown). This would have overestimated the role of AD in adult hand eczema, giving an OR of 4.1 instead of 1.9, due to recall bias in the retrospective design, and must be taken into account in future studies on adults that include a history of childhood AD. Furthermore, there is a need for improved and validated diagnostic criteria for AD that are useful for both children and adults.

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