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

Charlotte G. MORTZ, Klaus E. ANDERSEN and Carsten BINDSLEV-JENSEN
Department of Dermatology and Allergy Centre, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital, University of Southern Denmark, Odense, Denmark

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.

Accepted Apr 27, 2015; Epub ahead of print Apr 28, 2015
Charlotte G. Mortz, Department of Dermatology and Allergy Centre, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark. E-mail: Charlotte.moertz@rsyd.dk

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 passage 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-
The 897 participants 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 (44/215; 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 identified and 58 of these had cleared in less than 5 years (34 before 2 years of age, and 22 between 2 and 5 years of age). 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 & Rajka criteria (2), the lifetime prevalence was 34.1% (95% CI 31.0–37.2).

### 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)

<table>
<thead>
<tr>
<th>Baseline characteristics 1995</th>
<th>Participants 2010</th>
<th>Non-participants 2010</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56.3 (506)</td>
<td>38.4 (207)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>43.7 (393)</td>
<td>61.6 (332)</td>
<td></td>
</tr>
<tr>
<td>Present or past:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>23.9 (215/899)</td>
<td>16.9 (91/539)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Hand eczema</td>
<td>9.8 (88/899)</td>
<td>8.4 (45/539)</td>
<td>0.36</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>19.7 (177/899)</td>
<td>16.9 (91/539)</td>
<td>0.19</td>
</tr>
<tr>
<td>Asthma</td>
<td>12.0 (108/899)</td>
<td>11.3 (61/539)</td>
<td>0.69</td>
</tr>
<tr>
<td>Present:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact allergy</td>
<td>15.4 (120/778)</td>
<td>14.7 (54/368)</td>
<td>0.74</td>
</tr>
<tr>
<td>Positive specific IgEa</td>
<td>28.1 (171/609)</td>
<td>33.1 (86/260)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

| in Phase One 1,146 of the 1,438 participated in patch testing. | in Phase One 869 of the 1,438 participated in blood sample for IgE measurement. |

# 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 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).

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

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

In total 897 subjects answered the questionnaire; however, only 897 answered the questions on atopic dermatitis.
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 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).

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 mean that no more
Recall bias in atopic diseases

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 specificity 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.

ACKNOWLEDGEMENTS

This work was supported by Aage Bang’s Foundation, and Odense University Hospital Research Council.

The authors declare no conflicts of interest.

REFERENCES