Asthma from childhood to adulthood: asthma severity, allergies, sensitization, living conditions, gender influence and social consequences

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The course of asthma severity, clinical allergies, allergic sensitization, changes in living conditions and social outcome were studied prospectively over five follow-up visits from the mean age of 9 to 30 years in a cohort of 28 boys and 27 girls, selected randomly among asthmatic children attending a paediatric outpatient unit.

Asthma severity improved from childhood to adulthood, judged by symptom and medication scores and by the number of hospital admissions, but only nine subjects (16%) had been free from symptoms and medication over the last year of follow-up. After adolescence, asthma continued to improve among the males but not among the females. This difference could not be explained by gender differences in the course of clinical allergies or sensitization (skin-prick-tests and RAST) to common inhaled allergens, or by differences in environmental or social conditions. Sensitization to relevant perennial inhaled allergens correlated with asthma severity during adulthood. In general, clinical allergies and sensitization to inhaled allergens adopted during childhood persisted into adulthood. Approximately 10% of the subjects never adopted a clinical allergy or a positive allergy test. The social outcome was good.

Key words: adulthood; allergen exposure; allergy; asthma; childhood; course gender; history; long-term; prospective; sensitisation; smoking; social.

Introduction

Information from long-term follow-up studies of children with asthma is invaluable when educating patients and parents on the likely outcome of asthma and the future quality of life for the patient. Longitudinal studies on the course of asthma can also help us understand why the disease remains or resolves in different subjects, particularly when they include information on a wide range of possible influencing factors.

During childhood, asthma is more prevalent among boys than girls (1,2), whilst in adulthood asthma is more frequent among women (3,4). Female gender has been found to be an important risk factor for developing asthma in young adulthood (5) and, furthermore, there are studies indicating that asthma is more severe in adult females than males (6,7). Possible gender-related changes in asthma severity during the course of the disease from childhood to adulthood have not been reported in detail in previous prospective studies. Furthermore, it is not known if the gender difference in severity is related to the course and outcome of allergy and sensitization or to environmental factors.

Approximately 85% of asthmatic school children have concomitant allergy to inhaled allergens. Sensitization and clinical allergy to basic food stuffs like egg-white and cow’s milk develop mostly during infancy, and generally disappear after a few years (8–10). Reactions and sensitization to inhaled allergens generally appear later, and tolerance does not seem to develop during childhood or adolescence, as we have reported in earlier studies (9,10). It has not been made clear if or when tolerance to inhaled allergens develops during adulthood. In a previous report on the present cohort of 55 asthmatic children, we found a slight tendency to reduced clinical allergy to pollens but not to animal danders when the mean age of the group was 24 years (11). Whilst atopic allergy is a risk factor for asthma development and asthma severity in early childhood (12–15), the importance of associated clinical allergy and sensitization for asthma severity in older children and adults is not as clear (16–22).

Prospective, longitudinal studies are ideally suited to delineate the course of asthma. Participants in long-term follow-up studies on asthma may be recruited from patients attending health care facilities, from the general population or from birth cohorts. A large number of studies on the
course of asthma from childhood to adulthood incorporate several interim evaluations or include wide aspects on the course of the disease (25,26).

This is a report on the course of asthma in a cohort of 55 asthmatic school children, recruited from a paediatric outpatient unit and who attended all five follow-up visits over two decades up to the mean age of 30 years. Two interim reports have been published previously (11,27). The aims of the present study were to determine the course of asthma from childhood to adult life, taking into account disease severity, and associated clinical allergies and sensitization, to describe changes in living conditions, to assess social consequences from asthma, to study changes of lung function and to evaluate possible gender differences in these aspects. In this article we describe the course and outcome of all these variables except for lung function, which is reported in a companion paper (28).

**Study subjects**

The source for patient recruitment to this prospective study consisted of all asthmatic children \((n \approx 160)\) referred during the period from autumn 1973 to springtime 1976 to the Paediatric Allergy Outpatient Unit at the Central Hospital of Skövde, Sweden. This unit serves a geographically determined area and its population of approximately 200,000. The indications for referral from general practitioners and paediatricians to the unit were well established in the area, and stated that all children above the age of 3 years with a history of at least three episodes of wheezing should be referred for asthma and allergy evaluation. Three or more episodes of wheezing were used for a diagnosis of asthma in accordance with Buffum (29). This was a commonly used asthma criterion in Sweden during the 1970s. The routine work-up at the unit consisted of a history using a standardized questionnaire, scrutiny of all previous records, a physical examination and a skin-prick test (SPT).

A cohort of asthmatic children was randomly selected from the patients referred during this period with the intention to include half boys and half girls (for gender comparison) and to include patients who would be at least 7 years old, in order to be able to perform spirometry at the first follow-up, scheduled to 1977/78. Twenty-nine girls and 29 boys were asked to participate, but one girl and her parents did not give consent to follow-ups in addition to visits to her ordinary doctor, and one boy did not fulfill the criteria of asthma mentioned above. The remaining 56 children and their parents gave consent for the planned long-term follow-up, which was superimposed on their ordinary care programme and which was to include repeated SPTs, venous punctures for serum IgE antibody determinations, and spirometry before and after inhalation of salbutamol. Fifty-five of the 56 children fulfilling the inclusion criteria and giving consent reported for all five follow-up visits and this report encompasses these 55 subjects (Table 1). The fifty-sixth child, a girl, died during an asthma attack at the age of 16 years, between the second and third follow-up visits. At the initial visit to the unit (designated I) the mean age of the participants was 9 years. The study period from this visit, used for allocation, ranged over 21 years and included five follow-up visits, designated II–VI. The ages of the females and males were similar at all visits, but the interval from the previous visit differed slightly at visits II, IV and VI (Table 1). Onset of wheezing

<table>
<thead>
<tr>
<th>Visit no.</th>
<th>Visit year</th>
<th>Gender</th>
<th>Mean</th>
<th>Range</th>
<th>P</th>
<th>Mean</th>
<th>Range</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1974/76</td>
<td>M</td>
<td>9.2</td>
<td>5.7–14.4</td>
<td>n.s.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>9.6</td>
<td>4.7–13.8</td>
<td>n.s.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>II</td>
<td>1976/78</td>
<td>M</td>
<td>11.0</td>
<td>8.0–16.6</td>
<td>n.s.</td>
<td>1.8</td>
<td>0.5–3.2</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td></td>
<td>F</td>
<td>12.1</td>
<td>7.2–16.7</td>
<td>n.s.</td>
<td>2.5</td>
<td>0.6–4.1</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1978/80</td>
<td>M</td>
<td>13.1</td>
<td>9.9–18.5</td>
<td>n.s.</td>
<td>2.0</td>
<td>1.8–2.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>14.1</td>
<td>9.1–18.7</td>
<td>n.s.</td>
<td>2.0</td>
<td>1.8–2.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>IV</td>
<td>1983</td>
<td>M</td>
<td>17.2</td>
<td>13.9–22.7</td>
<td>n.s.</td>
<td>4.1</td>
<td>3.8–4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>17.2</td>
<td>12.7–21.8</td>
<td>n.s.</td>
<td>3.2</td>
<td>2.7–3.7</td>
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<tr>
<td>V</td>
<td>1990</td>
<td>M</td>
<td>24.3</td>
<td>21.1–29.7</td>
<td>n.s.</td>
<td>7.1</td>
<td>6.7–7.4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>F</td>
<td>24.2</td>
<td>19.5–28.9</td>
<td>n.s.</td>
<td>7.0</td>
<td>6.5–7.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>VI</td>
<td>1985/96</td>
<td>M</td>
<td>30.0</td>
<td>26.9–35.4</td>
<td>n.s.</td>
<td>5.7</td>
<td>5.4–6.0</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td></td>
<td>F</td>
<td>30.1</td>
<td>25.4–34.8</td>
<td>n.s.</td>
<td>5.8</td>
<td>5.5–6.0</td>
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</table>
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positive allergy tests. ‘Asthma severity’ was estimated from
regard to total serum IgE levels or the occurrence of
(31), but was judged solely by its appearance and without
with the suggestions by, for example, Hanifin and Rajka
typical morphology and distribution, thus in accordance
or chronic relapsing pruritic dermatitis with age-related
dermatitis’ (AD) was defined as a non-infectious, chronic
longer than eight hours in a hospital ward. ‘Atopic
A hospital ‘admission’ for asthma was defined as a stay
had continuous use of inhaled sodium cromoglycate
(inhaled corticosteroids were not prescribed at that time).

**DEFINITIONS**

A hospital ‘admission’ for asthma was defined as a stay
longer than eight hours in a hospital ward. ‘Atopic
dermatitis’ (AD) was defined as a non-infectious, chronic
or chronic relapsing pruritic dermatitis with age-related
typical morphology and distribution, thus in accordance
with the suggestions by, for example, Hanifin and Rajka
(31), but was judged solely by its appearance and without
regard to total serum IgE levels or the occurrence of
positive allergy tests. ‘Asthma severity’ was estimated from
visit II and onwards according to the frequency of wheezing
and the degree of medication reported from the 12-month
period prior to each follow-up. Severity was graded using a
symptom score (0–3 p) and a medication score (0–3 p),
producing a total asthma score of 0–6 p. ‘Symptom score’ 1
implies occasional wheezing in connection with respiratory
tract infections, heavy exposure to allergens, and/or hard
physical exercise. Symptom score 2 denotes wheezing up to
twice a week, and/or after ordinary physical exercise, such
as ordinary school athletics. Score 3 implies wheezing more
than twice a week and/or impairment of daily physical
activities. Score 0 denotes the absence of wheezing over the
whole year before the visit. ‘Medication score’ 1 implies
occasional use of bronchodilators for symptomatic relief
and/or the use of inhaled sodium cromoglycate or steroids
for less than 3 months a year over the year prior to the visit.
Medication scores 2 and 3 denote the use of bronchodila-
tors when needed and continuous use of one (score 2) or
two drugs (score 3) for asthma control. Score 0 implies no
use of anti-asthmatic medication over the year prior to the
visit. Over the whole study the general policy of medication
was similar, i.e. aiming at enabling the patient to take part
in all activities of ordinary life, including sports, without
wheezing. This implied that the patient should use one or
several drugs continuously for asthma control, in accor-
dance with the current pharmacology policy, if wheezing
occurred several times a week. ‘Clinical allergy’ was
estimated at all visits by questioning the occurrence of
clinical reactions to pollens, danders or food. Clinical
allergy against furred animals was defined as obvious
reactions from the eyes, the nose or the lower respiratory
tract within 1 h after exposure to a furred animal, and when
first reported such symptoms had to occur at least twice.
Clinical allergy to pollen was defined as obvious reactions,
not related to respiratory tract infections, from the eyes, the
nose or the lower respiratory tract during the pollen season
and when first reported, such symptoms had to occur for at
least two seasons to be noted. Current allergy to pollen
at the follow-up visits was defined as such symptoms during
at least one of the two preceding seasons and allergy to
animal danders was present if symptoms had occurred
during the last 12-month period. Allergy to food was
defined as obvious reactions which had occurred in the
respiratory or gastrointestinal tract or in the skin within
approximately 1 h after exposure, and had to occur twice
initially to be recorded.

These definitions are similar to those used in other
prospective, long-term cohort studies performed by us and
starting during the late 1970s and the 1980s (8–10). The
retrospectively obtained information on symptoms and
events occurring before joining the study was based on
patient records and standardized patients questionnaires
used in the unit at visit I. These data were scrutinized at
visit II especially with regard to the asthma and allergy
criteria, and living conditions.

**SKIN-PRICK TESTS**

SPTs were performed on the volar aspect of the forearm by
the same nurse at visit I to V and by another nurse,
educated by the previous nurse, at visit VI. Histamine
solution (10 μg·cm⁻²) and 0.9% saline were used as positive
and negative references, respectively. A weal with a mean
diameter (half the sum of the largest diameter and its
mid-point perpendicular) of more than 3 mm was denoted as positive, if the saline control was negative. Calculation of the discriminating power of histamine to saline was done at visit VI and showed diameters above 3 mm in all the histamine weals and in none of the saline weals. The mean diameter of the histamine weals was 6.7 mm and the coefficient of variation (CV) of duplicates was 14%.

At all visits the following allergens were tested: birch (Betula verrucosa), grass (Phleum pratense), cat (Felis domesticus), dog (Canis domesticus), horse (Equus caballus), house dust mites and moulds. Pollen and dander extracts (aqueous extracts, 1/20, w/v) were produced by Vitrum AB (Stockholm, Sweden) or ALK (Copenhagen, Denmark) in concentrations of 10 Heparin Equivalent Potency (HEP), corresponding to 10 000 biological units ml\(^{-1}\). Aqueous mould extracts (1/20, w/v) were used.

At visit VI the precision of SPT was evaluated by duplicate SPTs, using corresponding areas of the contralateral arm. The mean values (mm) of the weal diameters in subjects with positive reactions were 6.6 for birch, 7.9 for timothy, 8.8 for cat, 6.8 for dog, 8.1 for horse, 5.1 for D. pteronyssinus, and 4.2 D. farinae. The coefficients of variation, expressed as percentages of the mean diameter of the histamine weals and in none of the saline weals. The mean diameter of the histamine weals was 6.7 mm and the coefficient of variation (CV) of duplicates was 14%.

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A total of 148 admissions for asthma in 21 subjects were recorded from birth up to the last follow-up with 98% of the admissions recorded before the age of 16 years. During adulthood there were only two admissions, one each for a male and a female subject. During the period from birth to 5 years of age there was no gender difference (53 admissions in 14 subjects), whereas between 6 and 10 years of age nine males had 38 admissions and three females had nine admissions. Between 11 and 15 years of age, four males had 45 admissions and one female had one admission. An emergency visit for asthma was done by three males and two females over the year prior to visit V and by one male and two females during the year prior to VI. Three males and two females were sick listed for asthma over the year prior to visit V, in total 12 occasions. Over the year prior to visit VI, one male only had been sick-listed for asthma on a single occasion. All periods of sick-listing lasted less than 1 week.

**MEDICATION FOR ASTHMA**

Over the year before visit II, 15 subjects (27%) were on continuous asthma medication. At visit III, 24 subjects (44%) reported continuous medication to be compared with nine subjects (16%) at visit VI ($P<0.001$; OR 15.0; 95%CI 1.6–349.2). The most marked changes in medication seen over the 21-year period were exchange of oral β2-agonists for inhaled β2-agonists for occasional use, and exchange of inhaled sodium cromoglycate for inhaled corticosteroids for regular use. At the last follow-up, none took regular inhalations of cromoglycate, in contrast to 19 subjects at visit III. At visit VI, inhaled corticosteroids were used by seven subjects and another five subjects were recommended regular steroid use.

**GROWTH**

Mean heights for the male and female participants did not differ from Swedish normal standards (30) at visits II to V (Table 2). Height was not below $-1.9$ SD in any patient at any visit. Five males and three females showed an aberrant growth pattern, defined as a drop in height by more than one SDS between any two follow-up visits. In six subjects (five with mild asthma at all visits) such a decrease in height SDS occurred only between two subsequent follow-ups and final height was above $-1$ SD. Only one male subject (final height, $-1.4$ SDS) and one female (final height, $-0.5$ SDS) deviated continuously from the expected growth channel over several visits. The male patient had received repeated courses of oral steroids due to numerous emergency visits and the female patient had received local and short-term oral steroids for rheumatoid arthritis.

**TABLE 2. Height (standard deviation score; SDS) in 28 male (M) and 27 female (F) subjects obtained at visits II–V.**

<table>
<thead>
<tr>
<th>Visit no.</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>M</td>
<td>+0.2</td>
<td>+0.3</td>
<td>+0.1</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0.0</td>
<td>−0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>M</td>
<td>+1.7</td>
<td>+1.8</td>
<td>+1.6</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>+2.4</td>
<td>+2.1</td>
<td>+2.3</td>
</tr>
<tr>
<td>Minimum</td>
<td>M</td>
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</tr>
<tr>
<td></td>
<td>F</td>
<td>−1.5</td>
<td>−1.9</td>
<td>−1.9</td>
</tr>
</tbody>
</table>
ATOPIC ECZEMA

Onset of eczema was before the age of 2 years in 23 (retrospective data) of the 29 subjects who ever had eczema. In four subjects, eczema started after 7 years of age. The current frequency of atopic eczema varied between 18 and 33% at the six visits. The current rate of eczema decreased significantly from 33% at visit I to 18% at visit IV (P = 0.001; OR 14.0; 95% CI 2.2–115.4), and then increased to 31% at visit VI (P < 0.001). There were no gender differences either in current or cumulative rates of eczema. Severe atopic dermatitis in terms of need for frequent use of strong corticosteroid ointments and inconvenience in daily life was found in one female and one male subject at visit VI.

CLINICAL ALLERGY

There was no significant gender difference in the rates of allergy to pollens or furred animals at any visit. The course of clinical allergy to pollens and danders is shown in Fig. 2 A–B. Significant increase in allergy to pollens occurred from visit I (47%) to visit III (65%) for the whole group of males, females and both with reported allergy to furred animals over visit I–VI. (B). Percentage of males, females and both with reported allergy to pollens over visit I–VI. The current frequency of atopic eczema varied between 18 and 33% at the six visits. The current rate of eczema decreased from 33% at visit I to 18% at visit IV (P = 0.001; OR 14.0; 95% CI 2.2–115.4), and then increased to 31% at visit VI (P < 0.001). There were no gender differences either in current or cumulative rates of eczema. Severe atopic dermatitis in terms of need for frequent use of strong corticosteroid ointments and inconvenience in daily life was found in one female and one male subject at visit VI.

SPT AND RAST TO INHALED ALLERGENS

The frequencies of a positive SPT and RAST at the six visits to four common inhaled allergens are shown in Fig. 3 A–D. The changes of the prevalence of a positive RAST were analysed statistically only for visits III, IV, V and VI. There were no gender differences at any of the visits. The strength of sensitization at each of visits III to VI was also estimated by counting the number of positive SPTs to birch and timothy and calculating the proportions of positive SPTs out of all SPTs done to birch and timothy in females and males, respectively. Similar proportions were calculated for SPTs to three danders (cat, dog, and horse), for RASTs to three pollens (birch, hazel, and timothy) and for RASTs to three danders (cat, dog, horse). A significant gender difference in these proportions was found only once, at visit IV, and concerned the proportions of positive SPTs to pollens (males 64%, and females 41%; P = 0.023, OR; 2.6, 95% CI: 1.1–6.1). The rate of a positive SPT to birch pollen varied between 49% at visit III and 64% at visit VI (n.s.) and the rate of a positive RAST varied between 40% at visit II and 53% at visit VI (n.s.). The frequency of a positive SPT to timothy pollen varied between 55% at visit IV and 73% at visit III (n.s.) and the rate of a positive RAST to timothy varied between 55% at visit II and 69% at visit III (n.s.).

A significant decline of the rate of a positive RAST to cat allergen class 3–4 was seen from visit III to VI (51–33%, P = 0.039, OR; 4.0, 95% CI: 1.1–17.8). For dog allergen, we found a significant (P < 0.001, OR; 10.0, 95% CI: 2.3–61.9) increase in the frequency of a positive SPT from visit III (38%) to visit VI (71%), but over the same time period a significant (P = 0.014, OR; 4.0, 95% CI: 1.3–14.1) decrease was seen in the rate of a positive RAST from 60 to 47%. There were no significant changes over time for the rates of a positive SPT or RAST to horse or cow allergens.

The frequencies of a positive RAST to D. pteronyssinus at visits II to VI were; 13, 27, 7, 11 and 16% (n.s.) The number of subjects with a positive RAST of class 3–4 at any visit were; 1, 2, 3, 3, and 1. A positive RAST to D. farinae was found in six subjects (11%) at any of visits IV, V or VI (only tested at these visits), and in the same five subjects at all
three visits. All except one of the 15 positive RASTs were combined with a positive RAST to *D. pteronyssinus*. Evaluation for a sensitization to *L. destructor* was performed at visit V and disclosed only three subjects with a positive RAST. The frequencies of a positive RAST to moulds varied between 9 and 13% (n.s.).

RETAINING AND ADOPTING ALLERGY AND TEST REACTIVITY

The retention rates of clinical allergy and test reactivity between visit III at a median age of 13 years and at visit VI at a median age of 30 years are shown in Table 3. The number of subjects adopting or losing allergy or test reactivity is also given. Some important additional results are given here. The retention rate of clinical allergy from visit I to VI was 54% for pollens and 89% for animals. Twenty of the 21 subjects with both a positive SPT and RAST to birch pollen at visit III retained both a positive SPT and RAST at visit VI. Ten of the 13 subjects with a clinical allergy to pollens at visit III but not at visit VI retained a positive SPT and RAST to birch and/or timothy pollens at visit VI. Twenty-eight of the 30 subjects with both a positive SPT and RAST to cat allergen at visit III retained both a positive SPT and RAST at visit VI.

TOTAL SERUM–IGE

Total S-IgE concentrations are shown in Fig. 4. The proportions of values above an arbitrary upper normal limit of 100 kU l\(^{-1}\) were at the five follow-up visits, 69 (42 samples available), 72, 64, 49 and 60%. There was no gender difference between median serum IgE concentrations at any visit or between the number of males and females with abnormally high values. At visit III, 14 subjects had IgE values above 500 kU l\(^{-1}\) and 13 of them continued to have values above 100 kU l\(^{-1}\) throughout the study. At visit III, 15 subjects had values below 100 kU l\(^{-1}\) and 12 retained their values below 100 kU l\(^{-1}\) throughout. Twelve subjects (all with a positive SPT and RAST to both pollens and danders) had IgE above 1000 kU l\(^{-1}\) at one or more visits, and in six of these subjects the values remained at 500 kU l\(^{-1}\) or more throughout the study.
Clinical allergy to animal danders and pollens, to danders or pollens, or neither, was not associated to asthma severity. An association was found between severity and sensitization (RAST class ≥ 2) to the most important perennial allergens (cat, dog, horse); the proportion of subjects sensitized to all three allergens was higher (P < 0.01) among those with moderately severe or severe asthma than among those with none or mild asthma at visits IV (63 vs. 15%), V (41 vs. 3%) and VI (53 vs. 16%).

NON-ALLERGIC ASTHMA

Twelve subjects did not report an allergy to pollens and eight subjects to danders. Six of the 55 subjects (11%) did not report clinical allergy to pollens, danders or food at any visit. They did not demonstrate atopic dermatitis at any visit, with the exception of one subject, who had a mild and local eczema on one occasion. One subject once had a positive SPT to cat and a low RAST titre to dog and horse. Two of the six subjects had had total serum IgE levels above 100 kU l⁻¹ (maximum 239 kU l⁻¹). Asthma had been severe (total asthma score 5–6) in two, moderate in three (score 3–4) and mild in one subject. All six had been passively exposed to tobacco smoke during early childhood compared to 25 of the remaining 49 subjects (P = 0.030). Four of the six had been exposed to furred animals in their homes during childhood.

LIVING CONDITIONS, ALLERGEN AND TOBACCO EXPOSURE

The change in living conditions over the 21 years was similar in females and males (Table 4). The most obvious

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<tr>
<th>Allergy to</th>
<th>From III to VI</th>
<th>Retained at VI</th>
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<tr>
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<td>Pos. SPT to</td>
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<td>Dog</td>
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<tr>
<td>Horse</td>
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<tr>
<td>Any mite</td>
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<td>3</td>
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<tr>
<td>Any mould</td>
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</table>

TABLE 3. Clinical allergy and test reactivity in 55 subjects with childhood bronchial asthma. The number of subjects with allergy to pollens or danders, and the number with positive skin prick test (SPT) or RAST at visits III (mean age 13-1 years) and VI (mean age 30-1 years) are given. No. of subjects adopting, losing or retaining allergy or test reactivity between the visits are also shown, as well as the retention rates.

CLINICAL ALLERGY, SENSITIZATION AND ASTHMA SEVERITY

Clinical allergy to animal danders and pollens, to danders or pollens, or neither, was not associated to asthma severity. An association was found between severity and sensitization (RAST class ≥ 2) to the most important perennial allergens (cat, dog, horse); the proportion of subjects sensitized to all three allergens was higher (P < 0.01) among those with moderately severe or severe asthma than among those with none or mild asthma at visits IV (63 vs. 15%), V (41 vs. 3%) and VI (53 vs. 16%).

NON-ALLERGIC ASTHMA

Twelve subjects did not report an allergy to pollens and eight subjects to danders. Six of the 55 subjects (11%) did not report clinical allergy to pollens, danders or food at any visit. They did not demonstrate atopic dermatitis at any visit, with the exception of one subject, who had a mild and local eczema on one occasion. One subject once had a positive SPT to cat and a low RAST titre to dog and horse. Two of the six subjects had had total serum IgE levels above 100 kU l⁻¹ (maximum 239 kU l⁻¹). Asthma had been severe (total asthma score 5–6) in two, moderate in three (score 3–4) and mild in one subject. All six had been passively exposed to tobacco smoke during early childhood compared to 25 of the remaining 49 subjects (P = 0.030). Four of the six had been exposed to furred animals in their homes during childhood.

LIVING CONDITIONS, ALLERGEN AND TOBACCO EXPOSURE

The change in living conditions over the 21 years was similar in females and males (Table 4). The most obvious
change was the decreased domestic exposure to tobacco smoke and furred pets when the young adults moved away from home.

Six women but no men were active smokers at the last follow-up. CO in exhaled air from those who denied smoking at visit VI varied between 2 and 6 p.p.m. The values of the six smokers were: 38 p.p.m (20 cigarettes daily), 30 p.p.m (20 cigarettes daily and smoking husband), 23 p.p.m (15 cigarettes daily), 15 p.p.m (20 cigarettes daily and smoking husband), 12 p.p.m (10 cigarettes daily) and 4 p.p.m (10 cigarettes daily, but no smoking during 2 days before examination). The three females who started smoking in childhood continued smoking, while the two males who smoked during childhood stopped smoking before visit V.

By visit VI, at a mean age of 30 years, 45 subjects (82%) were married or lived in a marriage-like relationship and 27 (49%) had at least one child of their own. There were no gender differences in the degree of education or sporting activities. Five subjects (three males) had only compulsory school education, while 60% had at least 3 years of high-school training, and 12 females and nine males had university training. None were unemployed at visit V but five subjects (four females) reported that they were unemployed at visit VI, none of them due to asthma. At visits V and VI almost two-thirds of the subjects (similar for males and females) reported regular physical sport activities at least once a week. Such activities twice a week or more were reported by 25 subjects (13 males) at visit V and 20 subjects (10 males) at visit VI.

**Discussion**

In this study on the course of asthma over two decades in 55 asthmatic children, who were 5–14 years old when recruited, we found that asthma was initially more severe in boys than in girls, despite them having been recruited on the same criteria. The asthma course into adulthood was characterized by:

- A decreasing severity of asthma from adolescence, continuing in adulthood among the males but not in the females.
- A final body height within normal limits in both sexes.
- High rates of clinical allergy and sensitisation to pollens and furred animals and a high retention of this allergy and sensitisation in adulthood, similar in both sexes.
- A significant association between the extension of sensitization to furred animals and asthma severity in adulthood but not in childhood.

### TABLE 4. Living conditions and exposure to furred animals and tobacco smoke in 28 males (M) and 27 females (F) with childhood asthma, reported at six visits (visit no. I–VI) over 21 years. The number of subjects is given for males (M) and females (F) and both sexes combined

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• Occurrence of non-allergic asthmatics (approximately 10%) who remained non-allergic and non-sensitized during the whole study period.
• A substantial change for both sexes concerning living conditions in terms of decreasing rates of indoor furred animals and passive smoking.
• A successful social development concerning education, employment and physical activities in both sexes.

The patients recruited to this study had all been referred to the Central Hospital Outpatient Allergy Clinic from general practitioners or paediatricians in the province because of a history of three or more episodes of wheezing. At that time, all children in this county were expected to be referred for asthma and allergy evaluation when they presented with such a history, and an evaluation of the paediatric outpatient care in our area during the 1970s indicated that these recommendations were actually followed (32). We believe that the course of asthma in our cohort well reflects the course in school children diagnosed with asthma of various severity who attend a general hospital paediatric clinic. Thus, the course and outcome of our cohort differ from that of groups of infants and toddlers with wheezy bronchitis who have higher rates of remission (12), and also from population and birth cohort studies.

In comparison to some other prospective studies, the number of patients recruited to this study was low, and non-significant differences between, for example, males and females must be judged with caution. Nevertheless, we feel that the present study makes an important contribution to the knowledge about the prospects for asthmatic children, because all participants but one attended all five follow-up visits, which is important in delineating a course. Detailed information was obtained not only on asthma severity but also on allergies, living conditions and lifestyle, which could influence the course of asthma. The interview technique was uniform throughout the study, and one of the authors (B.K.) supervised or took part in the evaluations of all patients. Furthermore, the course of sensitization was judged not only with SPT but also with RAST, which is important since the quality of extracts used for SPT has improved considerably over the study period. The extracts used in the 1970s and during the first years of the 1980s were scarcely standardized, and the SPT results from that time should be interpreted with caution.

ASTHMA SEVERITY

The asthma improvement judged both by scores and hospital admissions for the whole group from childhood to adulthood agrees with observations made by other authors (25,26,33). A striking result was that statistically significant improvement of asthma judged by scores was limited to the males and that the non-significant tendency to improvement in females ceased after the age of 20 years. In a prospective long-term study from Melbourne, Kelly et al. reported that asthma had worsened between the age of 21 and 28 years in 28% of the men and 19% of the women (26), whereas Roorda et al. (34), who followed 406 asthmatic children to an age of 21–29 years, found that the men had more symptoms than the women at that age. In a questionnaire follow-up study of children from Tasmania, Jenkins et al. reported that being female was the most common risk factor for having asthma as an adult (35). Also, in a re-investigation of asthmatic children at an age of 22–33 years, Gerritsen and co-workers found that the women tended to have a higher rate of current symptoms (36).

The more favourable course and outcome among the men than among the women could not be explained by less domestic allergen exposure, different medication or better social course and outcome, nor by a lower degree of clinical allergy or sensitization to common inhaled allergens. Neither could it be explained by more favourable living conditions during childhood. A diverging factor was that all adult males were non-smokers, whereas six adult females were moderate cigarette smokers. These females had only mild or moderate asthma, and an exclusion of them from the calculations did not change the trends but they reported slightly higher symptom scores and somewhat lower medication scores than the non-smoking women. Whether this gender difference in the course of asthma severity is supported by lung function data is analysed in the companion paper (28).

Despite asthma improvement for the group as a whole, only nine subjects (16%) had been free from asthma symptoms and medication during the year prior to the last follow-up. If the criterion for complete remission of asthma is absence of symptoms and medication both at the last and the penultimate visit, only six of the 55 participants (11%) would be considered free from asthma. Cure rates of 20–80% have been reported, and differences in, for example, the definitions of cure, severity of asthma at inclusion, environmental factors, and techniques for follow-up (e.g. interview or self-administered questionnaires) presumably account for this variability (23,24). These high rates of persistent asthma may reflect the base for recruitment (a hospital outpatient clinic) and the fact that all participants were interviewed.

The aim with medication was similar throughout the study period but marked changes were seen in the use of different pharmaceutical agents and in the routes of administration, reflecting the ‘historical’ development in this field. The contribution of such changes to the course of asthma in this cohort cannot be estimated, but apparently the change of medication did not withhold the tendency to worsening of the asthma among the adult females.

ALLERGY AND SENSITIZATION

The preponderance of sensitization to pollens and animal danders over mites and moulds agrees with previous studies from inland or northern areas of Sweden (37,38) and with the results in some cohorts of children from our province followed from birth to middle school age (9,10). Tolerance to inhaled allergens developed only in a few subjects from childhood to adulthood, with either being judged from
clinical symptoms: SPT, RAST, or SPT and RAST. The fact that the great majority of the subjects did not have domestic contact with furred animals after adolescence did not result in lowered sensitization rates to such animals. Low-dose exposure from indirect contacts with animal danders is frequent, and thus seems able to maintain clinical allergy and sensitization (39–41). The improvement of asthma symptoms seen from childhood to adulthood cannot be explained by development of tolerance to inhaled allergens, but the reduced domestic exposure to furred animals after childhood, similar in both sexes, may have contributed to the improvement.

The low rate of clinical allergy and sensitization to egg allergens, found in adulthood, fits well with findings in previous studies of an early development of tolerance to such allergens and that this tolerance remains (9,10). The high incidence in adulthood of clinical allergy to nuts, peanuts and fruits with an association to birch pollen sensitization and with a dominance of solely an oral allergy syndrome is consistent with previous observations (42–45).

The genetic influence on the IgE production is obvious from the fact that high levels of serum total IgE mostly remained high, and low values remained low during the whole follow-up. The genetic heterogeneity of childhood asthma is illustrated by the fact that six subjects never developed clinical allergy and that five of these never had evidence of sensitization. The occurrence of a non-allergic asthma has been reported previously (20,21), and the present finding that approximately 10% of the children remained non-allergic and non-sensitized over such a long period with repeated checks is a strong evidence of the existence of a true non-allergic type of asthma in school-aged children.

LIVING CONDITIONS

The high number of subjects living in rural area, in one-family houses and with daily contact with furred animals during childhood and youth agrees well with the results that we obtained in an inquiry among all 40 000 school children in our province in the late 1970s (1). Our routine recommendations since the 1970s to avoid keeping furred pets in the homes of asthmatic children were only partly acted upon during childhood and adolescence. Our general impression of good social adaptation in adult life was supported by the data on education, the low unemployment rate and the high rate of physical exercise. The percentage of subjects with university training was slightly higher than average for our province, and the unemployment rate was slightly below Swedish national figures from that time. Our finding of a good social adaptation agrees with the report from Ross et al. (46).

CONCLUSIONS

This study has shown that asthma generally improves from childhood to adulthood, that clinical allergies and sensitization to inhaled allergens generally persist, and that the social outcome is good. While asthma continuous to improve after adolescence in the males, it seems to worsen among the females, and this difference cannot be explained by gender differences in the presence and course of clinical allergies, sensitization to common inhaled allergens, or social and environmental conditions.

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