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

B. Kjellman and P. M. Gustafsson

Department of Paediatrics, Central Hospital, Skövde, Sweden

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.

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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

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Correspondence should be addressed to: Dr Bengt Kjellman, Department of Paediatrics, Central Hospital, S-541 85 Skövde, Sweden. Tel: + 46 500 43 10 00; Fax: + 46 500 43 28 25.

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course of asthma from childhood to adult age have been published and were reviewed by Roorda (23) and by Grol *et al*. (24). Several studies on asthma outcome suffer from not being prospective (33 of 55 studies in the Grol review) or from being only questionnaire-based (28 of 55 studies the in Grol review). Other studies included highly selected groups of asthma patients, included only single or a few follow-up sessions, or had lost many patients at follow-up. Few prospective long-term studies on 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 fulfil 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 1. Visit year, age of subjects, and interval between six visits (I–VI) in the follow-up study of 28 males and 27 females with childhood asthma. Statistical evaluations refer to comparisons between males and females

			Age (years)			Interval from previous visit (years)		
Visit no.	Visit year	Gender	Mean	Range	*P*	Mean	Range	*P*
I	1974/76	M	9·2	5·7–14·4		—	—	
		F	9·6	4·7–13·8	n.s.	—	—	
II	1976/78	M	11·0	8·0–16·6		1·8	0·5–3·2	
		F	12·1	7·2–16·7	n.s	2·5	0·6–4·1	$<0{\cdot}05$
III	1978/80	M	13·1	9·9–18·5		2·0	1·8–2·3	
		F	14·1	9·1–18·7	n.s.	2·0	1·8–2·1	n.s.
IV	1983	M	17·2	13·9–22·7		4·1	3·8–4·6	
		F	17·2	12·7–21·8	n.s.	3·2	2·7–3·7	$<0{\cdot}001$
V	1990	M	24·3	21·1–29·7		7·1	6·7–7·4	
		F	24·2	19·5–28·9	n.s.	7·0	6·5–7·6	n.s.
VI	1985/96	M	30·0	26·9–35·4		5·7	5·4–6·0	
		F	30·1	25·4–34·8	n.s.	5·8	5·5–6·0	$<0{\cdot}001$

was before 2 years of age in 47% of the subjects, and between 2 and 7 years in 42% (retrospective data) according to information obtained at visit I, supported by various health records, and confirmed at visit II. All children had experienced at least one episode of bronchial obstruction the year prior to visit I. At this visit the occurrence of atopic dermatitis was 37% in the girls and 30% in the boys (n.s.), and of seasonal rhinitis 44% in the girls and 39% in the boys (n.s.). Four girls and four boys had continuous use of inhaled sodium cromoglycate (inhaled corticosteroids were not prescribed at that time).

Methods

At all visits (I–VI) a history was taken using a standardized questionnaire emphasizing the frequency and severity of asthmatic symptoms, allergic reactions and other atopic manifestations, and environmental and social issues. One of the authors (B.K.) participated in the evaluations throughout the study. Records from visits to well-baby clinics, outpatient clinics or from hospital wards, before as well as during the study, were scrutinized. A physical examination, and SPT to common inhaled allergens were undertaken at all visits. Total serum IgE and specific serum IgE antibody concentrations to inhaled allergens and lung function were determined at visits II–VI. For routine check-ups for asthma and allergy between the follow-up visits the patients attended their ordinary doctors (general practitioners or paediatricians). With a few exceptions, the examinations were performed during late autumn, winter or early spring before the pollen season. The visits were timed to allow the patients to be in optimal condition. *Height* was measured at each follow-up with a stadiometer, and the deviation from predicted height for age and sex was calculated and presented as standard deviation scores (SDS) (30). Aberrant growth was arbitrarily defined as a drop in height of at least one SDS between any two follow-up visits. Two examinations were added during the follow-up period: home visits by a trained and experienced allergy nurse in connection with visit III; and determinations of carbon-monoxide concentrations in exhaled air at visit VI by use of a portable CO-analyser (CO Monitor, Bedford Scientific Ltd, U.K.).

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 bronchodilators 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 accordance 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 (10g l^{-1}) 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 verucosa*), grass (*Phleum pratense*), cat (*Felis domesticus*), dog (*Canis domesticus*), horse (*Equus cabellus*), house dust mites and moulds. Pollen and dander extracts (aqueous extracts, 1/10 w/v) produced by Vitrum AB (Stockholm, Sweden) were used at visit I. Extracts from Dome Hollister Stier, UK (500 protein nitrogen units ml^{-1}) were used at visits II and III. At visits IV to VI the extracts used were produced by Pharmacia Diagnostica (Uppsala, 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 were 23 for birch, 19 for timothy, 24 for cat, 15 for dog, 24 for horse, 20 for *D. pteronyssinus* and 14 for *D. farinae*. A change from a positive to a negative test or *vice versa* in the duplicate testing was seen in the following number of subjects: three for birch, two for timothy, one for dog, cat and horse, respectively, and none for mites.

SERUM LEVELS OF TOTAL AND SPECIFIC IGE

These tests were done from visit II onwards in the same laboratory (Department of Clinical Chemistry/Lab Novo-Calab, Central Hospital, Skövde) and by the same assistants. Due to an administrative error, the first 14 serum specimens were lost at visit II. Total serum IgE concentrations were estimated with the Phadebas PRIST (Pharmacia Diagnostica, Uppsala, Sweden) from visits II to V, and with the Phadebas CAP method at visit VI (paper discs were not available). The CVs for IgE determinations in our laboratory varied between 10 and 15% during the late 1970s and the 1980s, and was 8·4% at visit VI, based on duplicate tests from the first 15 subjects investigated. Specific serum IgE antibodies were determined with Phadebas RAST (Pharmacia Diagnostica, Uppsala, Sweden) except for one allergen (horse) on one occasion (visit VI), when the Phadebas CAP method was used (paper discs not available). The RAST class rating 0–4 was used, i.e. a positive RAST implies an arbitrary concentration of $\geq$0·35 PRU ml^{-1}. The further limits were: 0·70, 3·5 and 17 PRU ml^{-1}. IgE antibodies to the following antigens were determined at visit II to VI: birch, timothy, hazel, dog, cat, horse, cow, *D. pteronyssinus* and moulds. Tests for *D. farinae* were added from visits IV to VI, and at visit V tests for Lepidoglyphus destructor. At visit VI all sera were also analysed for IgE antibodies to egg-white.

During the late 1970s and during the 1980s, the CVs for RAST obtained in this laboratory varied between 15 and 24%. At visit VI duplicate RASTs were analysed in the first 10 subsequent subjects for the following allergens: birch, dog, cat, *D. pteronyssinus*, *D. farinae*, the mould mixture and for horse allergen. The number of subjects with a change from positive to negative or *vice versa* was one for birch and one for dog (from 0·40–0·30 PRU ml^{-1}) and none for the remaining allergens. The number of subjects with a change from one RAST-class to another was one for cat (3·6 to 3·4 PRU ml^{-1}) and one for *D. pteronyssinus* (0·8–0·6 PRU ml^{-1}).

STATISTICS

Equality between non-paired proportions was asessed with the χ^2-test or the Fisher's exact test if an expected cell value was less than five. The McNemar's test was used for paired observations. The *P*-values, the odds ratios (OR) and the 95% confidence intervals (CI) are given. Analysis of equality between unpaired sets of data were calculated with the Mann–Whitney test and between paired sets with the Wilcoxon matched pairs signed ranks test. Not significant (n.s.) implies a $P \geq 0{\cdot}05$.

ETHICS

The ethical committee at the Central Hospital in Skövde initially approved the study. During childhood and adolescence the children and their parents gave their informed consent before every follow-up. In adulthood, informed consent was received from all study subjects.

Results

ASTHMA SCORES

For the whole group the *total asthma scores* (Fig. 1) peaked at visit III and then declined over the subsequent follow-up visits. The increase from visit II to III was not significant. From visit III, total asthma scores decreased significantly to visit IV ($P = 0{\cdot}039$), visit V ($P = 0{\cdot}02$) and visit VI ($P = 0{\cdot}002$). Significant reductions were also seen from visit II to VI ($P = 0{\cdot}005$) and from visit IV to VI ($P = 0{\cdot}013$). For the males, the total asthma scores dropped subsequently from visit III. The decline to visit VI was significant from visit II ($P < 0{\cdot}001$), III ($P < 0{\cdot}001$), IV ($P = 0{\cdot}003$) and V ($P = 0{\cdot}004$). Among the females, a significant increase in total asthma score was seen from visit II to III ($P = 0{\cdot}033$), and tendencies to reduced total asthma scores were seen from visit III to visits IV and V, but in contrast to the findings among the males total scores tended to increase among females from visit V to VI.

The *symptom scores* in males decreased significantly from visit II ($P = 0{\cdot}005$), III ($P = 0{\cdot}032$), and V ($P = 0{\cdot}037$) to visit

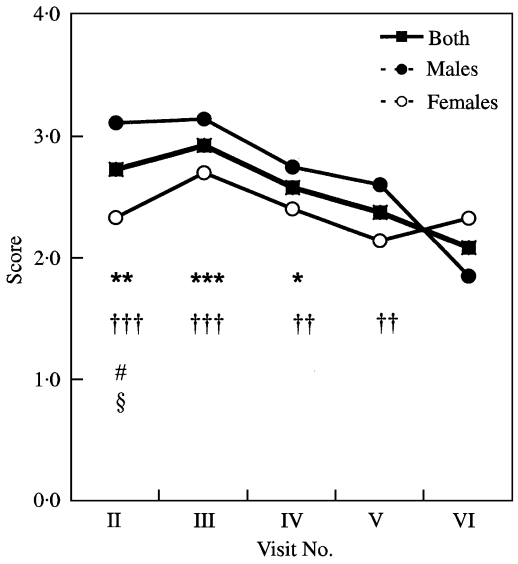

FIG. 1. Mean total asthma scores for males ($n=28$) and females ($n=27$) and both sexes combined from visit II to VI. For definitions see Methods.
$^{*}P<0{\cdot}05$; $^{**}P<0{\cdot}01$; $^{***}P<0{\cdot}001$, visit II–V *vs.* visit VI, both sexes. $^{\dagger\dagger}P<0{\cdot}01$; $^{\dagger\dagger\dagger}P<0{\cdot}001$, visit II–V *vs.* visit VI, males only. $^{\#}P<0{\cdot}05$ visit II *vs.* III, females only. $^{\S}P<0{\cdot}05$, males *vs.* females, visit II.

VI and *medication scores* also declined gradually in the males from visit III ($P<0{\cdot}001$), IV ($P=0{\cdot}003$), and V ($P=0{\cdot}01$) to VI. Among females, the symptom and medication scores did not change significantly over the follow-up.

Total asthma scores and medication scores tended to be higher in the males than in the females over visits II to V (significantly higher symptom scores in males at visit II, $P=0{\cdot}036$), but at visit VI the reverse was found, i.e. all scores tended to be higher in the female group.

The number of males without symptoms or medication increased from one at visit II to seven at VI, to compare with one woman at visit II and two women at VI. Six of the nine subjects with an asthma score of 0 at visit VI were also free from asthma at V.

HOSPITAL ADMISSIONS, EMERGENCY VISITS AND SICK LISTING

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 ($P<0{\cdot}001$; 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 β_2-agonists for inhaled β_2-agonists for occassional 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 $-1{\cdot}9$ 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 SDS. Only one male subject (final height, $-1{\cdot}4$ SDS) and one female (final height, $-0{\cdot}5$ 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 rheumtaoid arthritis.

TABLE 2. Height (standard deviation score; SDS) in 28 male (M) and 27 female (F) subjects obtained at visits II–V. Mean, maximum and minimum values are given

		Visit no.			
		II	III	IV	V
Mean	M	+0·2	+0·3	+0·1	+0·2
	F	0·0	−0·1	0·0	0·0
Maximum	M	+1·7	+1·8	+1·6	+1·7
	F	+2·4	+2·1	+2·3	+2·3
Minimum	M	−1·0	−1·1	−1·1	−1·3
	F	−1·5	−1·9	−1·9	−1·9

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 ($P=0{\cdot}001$; OR 14·0; 95% CI 2·2–115·4)), and then increased to 31% at visit VI ($P<0{\cdot}001$). 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 ($P=0{\cdot}016$; OR: 6·0, 95%CI: 1·28–38·78), mainly due to an increase for the males ($P=0{\cdot}041$). Significant decrease in allergy to pollens occurred from visit III (65%) to V (47%; $P=0{\cdot}034$, OR: 3·5, 95% CI 1·08–12·56), mainly due to a decrease for the males ($P=0{\cdot}027$, OR: 5·50, 95% CI: 1·16–35.89). Clinical allergy to furred animals varied between 65% (visit I) and 78% (visit IV; n.s.).

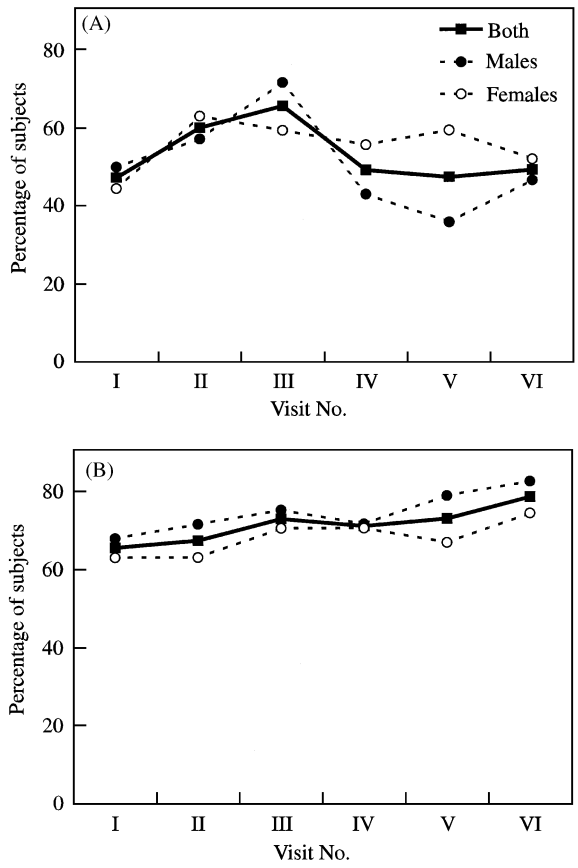

FIG. 2. (A) Percentage of males, females and both with reported allergy to pollens over visit I–VI. (B). Percentage of males, females and both with reported allergy to furred animals over visit I–VI.

At visit VI clinical allergy was found to nuts and/or peanuts in 20 subjects (17 with a positive SPT to birch pollen), to fruits in 17 subjects (15 with a positive SPT to birch pollen) and to carrots in four subjects (all with a positive SPT to birch pollen). Fifteen of these 21 subjects reacted with oral allergy symptoms only. All 55 adult subjects tolerated cow's milk, and only one had an allergy to eggs (RAST, 5·9 PRU ml^{-1}). Furthermore one subject had a positive RAST to egg-white (1·0 PRU ml^{-1}).

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%; $p=0{\cdot}023$, 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%, $P=0{\cdot}039$, OR; 4·0, 95%CI; 1·1–17·8). For *dog* allergen, we found a significant ($P<0{\cdot}001$, 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 ($P=0{\cdot}014$, 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

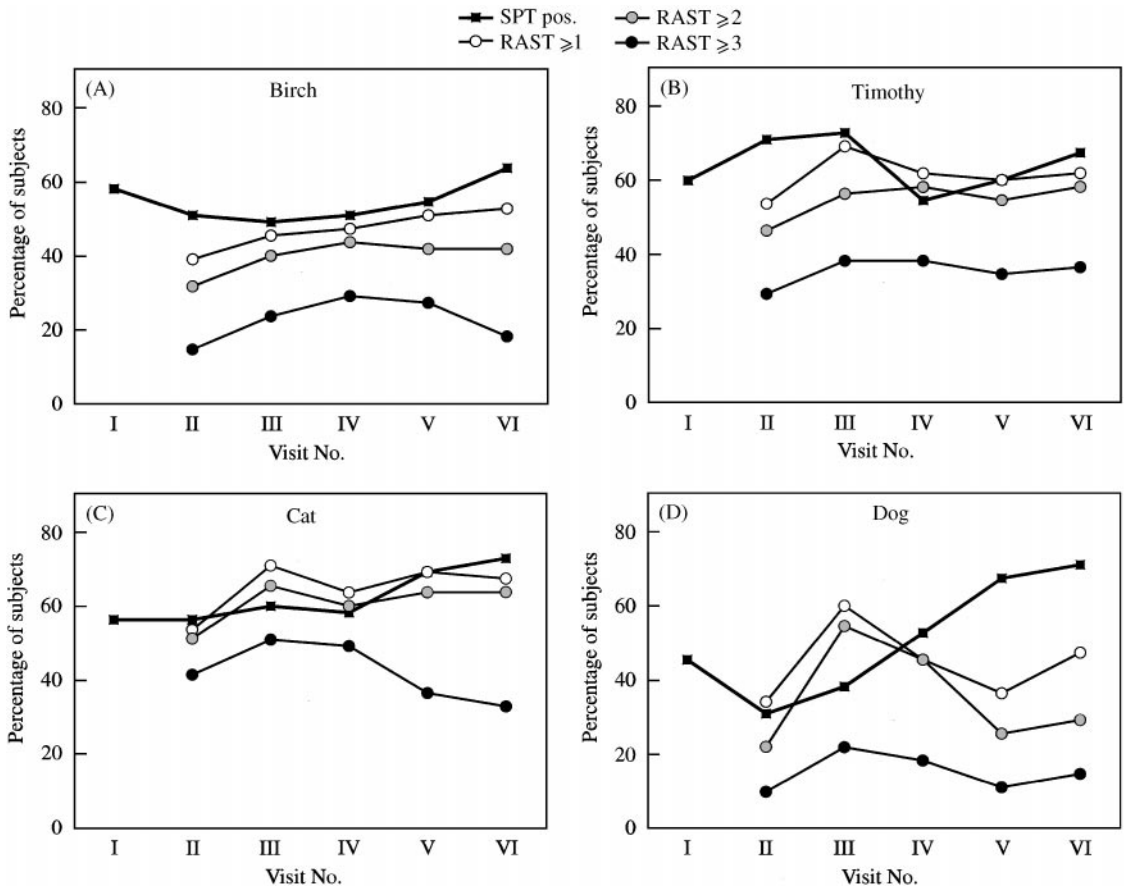

FIG. 3. (A) Percentage of subjects with positive skin prick test (SPT) or RAST to birch pollen over visit I–VI. (B) Percentage of subjects with positive skin prick test (SPT) or RAST to timothy pollen over visit I–VI. (C) Percentage of subjects with positive skin prick test (SPT) or RAST to cat dander over visit I–VI. (D) Percentage of subjects with positive skin prick test (SPT) or RAST to dog dander over visit I–VI.

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.

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

	At III (*n*)	At VI (*n*)	From III to VI		Retained at VI (*n*)	Retention at VI (%)
			Adopted (*n*)	Lost (*n*)		
Allergy to						
Pollens	36	27	4	13	23	64
Danders	40	43	6	3	37	93
Pos. SPT to						
Birch	27	34	10	3	24	89
Timothy	41	37	2	6	35	85
Cat	34	40	8	2	32	94
Dog	22	39	19	2	20	91
Horse	36	33	4	7	29	81
Any mite	6	13	10	3	3	50
Any mould	2	8	7	1	1	50
Pos. RAST to						
Birch	25	29	5	1	24	96
Timothy	38	34	4	8	30	79
Cat	39	37	3	5	34	87
Dog	32	26	3	9	23	72
Horse	33	28	6	11	22	67
D. Pter.	15	9	3	9	6	40
Any mould	21	6	1	15	5	24

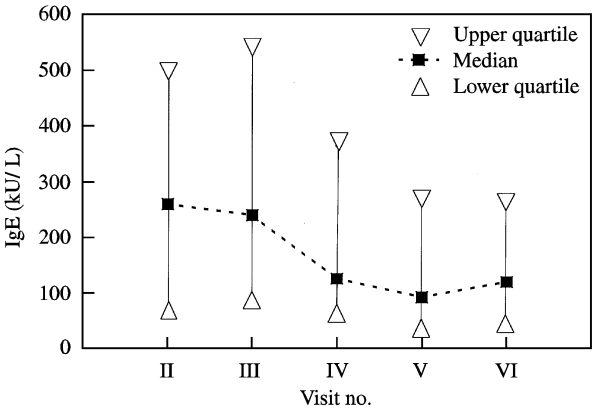

FIG. 4. Total IgE serum concentrations over visit II–VI. Median values and upper and lower quartiles are given.

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$\geq$2) to the most important perennial allergens (cat, dog, horse); the proportion of subjects sensitized to all three allergens was higher ($P<0{\cdot}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 ($P=0{\cdot}030$). 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

		Visit no.					
Living/exposure		I	II	III	IV	V	VI
Rural living	M	13	14	13	10	6	5
	F	11	12	11	7	7	9
	Both	24	26	24	17	13	14
One-family house	M	26	27	26	24	8	10
	F	20	21	23	15	6	16
	Both	46	48	49	39	14	26
Domestic furred pets	M	13	7	6	4	1	3
	F	17	8	7	4	1	3
	Both	30	15	13	8	2	6
Stable/riding	M	3	2	1	1	1	0
	F	4	5	3	3	1	3
	Both	7	7	4	4	2	3
Cow house	M	5	5	4	2	1	1
	F	5	3	3	3	0	1
	Both	10	8	7	5	1	2
Passive smoking	M	–	16	16	6	—	0
	F	–	15	15	7	—	2
	Both	–	31	31	13	—	2
Active smoking	M	0	1	2	1	0	0
	F	0	2	3	4	5	6
	Both	0	3	5	5	5	6

- 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 life style, 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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