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REVIEW

Outcome of asthma: longitudinal changes in lung function

C.S. Ulrik

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ABSTRACT: Current knowledge about factors determining outcome of asthma is limited, but observations over the last few decades suggest that active asthma has a negative impact on the longitudinal changes in lung function. This review aims to give an overview of the present knowledge concerning longitudinal changes in lung function, including clinical markers for distinctly poor outcome with regard to lung function, in children and adults suffering from asthma.

The majority of patients with asthma have a good prognosis. However, some patients with asthma, especially those with more severe disease, are at risk of impaired growth of lung function during childhood, a lower maximally attained level of lung function and excessive decline in lung function in adulthood, which may lead to life-threatening lung function impairment. Clinical markers of poorly controlled airway inflammation appear to have a negative impact on the longitudinal changes in lung function, and disease progression to nonreversible airflow obstruction may be observed in a minority of patients with asthma.

Early intervention with anti-inflammatory therapy may improve the short-term outcome of asthma, but long-term controlled studies are clearly needed in order to verify whether or not treatment, especially with inhaled corticosteroids, according to the current international guidelines alters the natural history of asthma, *i.e.* disease progression with regard to changes in lung function and possible development of nonreversible airflow obstruction.

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Correspondence: C.S. Ulrik
Virum Overdrevsvej 13
DK-2830 Virum
Denmark
Fax: 45 45836331

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Asthma is one of the most common chronic diseases in both children and adults, and evidence from recent years suggests that the occurrence of asthma is on the increase in many industrialized countries, not least in children and adolescents [1, 2]. The origins of asthma are obscure, and, although major advances in our understanding of asthma have occurred in recent years, many questions remain largely unanswered, particularly those concerning factors that determine the outcome of asthma. Recent studies have revealed that bronchial biopsies from patients suffering from asthma are characterized by: 1) shedding of the surface epithelium, 2) thickening of the reticular basement membrane, 3) thickening of the bronchial smooth muscle, 4) glandular hyperplasia, and 5) marked cellular infiltration, in most cases dominated by eosinophils. The latter points to the critical importance of both acute inflammation and airway remodelling due to chronic inflammation for disease progression in asthma or, in other words, that the key to successful management of asthma may depend upon early and effective anti-inflammatory treatment, before airway remodelling has time to get a hold and permanently alter airway function.

Current asthma status may be described, especially by patients, in terms of the presence or absence of symptoms, quality of life or minimum use, if any, of antiasthma medication. But for the clinician, disease control is also characterized by best possible level of lung function and absence of signs of poorly controlled airway inflammation. In line with this, studies of asthma outcome relying on questionnaire data alone are more likely to be retrospective, susceptible to recall bias and difficult to compare owing to the use of different questionnaires. Another problem is the well-known poor correlation between perceived severity of asthma symptoms and degree of underlying airflow obstruction [3], as determined by the forced expiratory volume in one second (FEV_1), which is observed not least in subjects with mild-to-moderate disease. Objective assessment of disease status, and change therein, is therefore a *sine qua non* for the evaluation of disease progression in asthma. Available studies on the outcome of asthma are therefore only included in the present review provided that objective measurements of airway function, *e.g.* spirometry, have been obtained.

Cross-sectional studies have consistently shown that lung function in patients with clinical asthma is less than predicted [4–6], which, besides suboptimal treatment at the time of measurement, may reflect, depending on the age of the patient, any combination of at least four factors: 1) slower growth of lung-function; 2) lower maximally attained level of lung function; 3) earlier onset of decline of lung function; and 4) accelerated decline of lung function. The identification of factors having an, especially negative, impact on each of these phases of the respiratory life cycle are therefore of crucial importance for the understanding of disease progression and prognosis in asthma.

This paper aims to give an overview of the longitudinal changes in lung function, including clinical markers of distinctly poor outcome with regard to lung function, in children and adults with established non-occupational asthma.

Longitudinal changes in lung function

Observations over the last few decades suggest that the longitudinal changes in pulmonary function, in both children and adults with persistent asthma, are less favourable than what is seen in the nonasthmatic population [4, 7, 9].

There is a paucity of longitudinal data relating to growth of lung function in children with asthma, but a number of the available studies suggest that growth of lung function in persistent symptomatic children is parallel to, but at a lower level than that in nonasthmatic children [9–12]. However, a recent population-based study by WEISS *et al.* [8] has shown that persistent active asthma has a progressive negative impact on the annual change in FEV1 in young females, suggesting an even greater negative effect of childhood asthma on the maximally attained level of lung function. Thus, although previous studies of lung function in symptom-free adults with a history of childhood asthma have, in most cases, observed discrete abnormalities of lung function [10–14], it seems reasonable to conclude that asthmatic children and adolescents, even if their asthma goes into remission for a shorter or longer period of time, are at risk for remaining at a disadvantage with respect to lung function when they reach adulthood.

Longitudinal studies of adults suggest that the rate of decline in lung function in patients with asthma is greater than that in the nonasthmatic population [5, 7, 15]. The magnitude of the excess loss of lung function, however, differs between the studies, but most studies have reported an excess decline in FEV1 of 5–25 $mL \cdot yr^{-1}$. Subjects with mild asthma are likely to be under-represented in these studies, and it seems likely that mild asthma may be associated with almost normal rates of decline in lung function. The available information, however, indicate that more severe asthma is likely to be associated with an excess annual decline in lung function.

Potential markers for increased risk of unfavourable longitudinal changes in lung function in children and adults suffering from asthma are discussed below. Longitudinal studies of asthmatics comprising at least one assessment of lung function are listed in table 1 [4, 5, 7, 8, 10, 11, 13, 16–52].

Sex

A male excess is usually found in the prevalence of childhood asthma, but with the onset of puberty asthma incidence becomes higher among females compared with males [53–55] and remains higher throughout adulthood [54–56], which cannot be explained by diagnostic bias [54]. However, the effect of sex on the outcome of asthma is not clear. The presently available literature on this topic comprises seven studies that showed no effect of sex on the long-term outcome of asthma [22, 29, 34, 35, 41, 44, 49]. One study found females to have a better prognosis than males [27], and four studies reported that females had a worse prognosis than males [8, 11, 19, 42].

In the study by WEISS *et al.* [8], a population-based cohort of 602 children, initially aged 5–9 yrs, were examined annually for 13 yrs. The total number of children reporting doctor-diagnosed asthma over the course of the study was 67 (42 males). For females, the effect of active asthma was negative and statistically significant for growth in FEV1, whereas active asthma was not a significant predictor for change in FEV1 in males. Active asthma had a negative effect on change in forced mid-expiratory flow ($FEF_{25-75\%}$) in both males and females. From the analyses, the authors predicted that a female who develops asthma at 7 yrs of age would experience a 5% reduction in FEV1 by 10 yrs of age and a 7% deficit by 15 yrs of age. Inactive asthma was not a significant predictor for change in lung function. These observations suggest that sex has a significant impact on longitudinal changes in lung function in subjects with persistent asthma, although the findings might be confounded by the severity of disease as female asthmatics were more likely to be hospitalized for asthma than male asthmatics.

In a 10-yr follow-up of 46 children (24 males) with atopic asthma and 24 children (7 males) with nonatopic asthma recruited from an outpatient clinic, ULRIK *et al.* [9] found no significant effect of sex on the level of FEV1 % predicted in early adulthood. Likewise, PANHUYSEN *et al.* [49] reported from a 25-yr follow-up of 181 adult asthmatics (aged 13–44 yrs at enrolment; 57% males) that sex was not a significant determinant for the presence or absence of current respiratory symptoms, FEV1 <90% pred or airway hyperresponsiveness at the end of the study period. From a follow-up study of a hospital-based cohort of 101 children (70 males) with asthma (6–14 yrs of age at enrolment, re-examined after a mean period of 16 yrs), GERRITSEN *et al*. [29] reported that the outcome of childhood asthma (level of FEV1 % pred in adulthood) does not appear to be related to sex. However, GODDEN *et al.* [44] reported from a 25-yr follow-up of 121 children with asthma recruited from a random community survey that females had greater airway responsiveness than males, although sex had no effect on outcome in relation to symptoms.

To draw a conclusion concerning the possible impact of sex on longitudinal changes in lung function in asthmatics, based on the available studies, is very difficult. Most of the studies point to no effect of sex on outcome; however, some studies by WEISS *et al.* [8] suggest that female sex may be associated with a worse prognosis. Subjects with moderate-to-severe asthma are likely to be over-represented in hospital-based cohorts, as suggested by the relatively high proportion of females in most of the cohorts studied, which may further complicate the interpretation of the findings with regard to a possible causal relationship between sex and outcome of asthma. However, the frequency of hospital admissions for asthma and the mean duration of hospital stays for asthma are higher for females than for males [57], suggesting that asthma may be more severe among females, and recent evidence from a study by TROISI *et al.* [58] suggests that oestrogen plays a role in the pathophysiology of asthma. Furthermore, as previously mentioned, nonatopic asthma is more prevalent in young females than in young males, and evidence from at least two studies suggests that the outcome with regard to lung function is worse for patients with nonatopic asthma than for those with atopic asthma [26, 35, 46]. There is, therefore, some evidence that female sex is associated with a worse outcome, although this association might be caused by confounding by severity and possibly also the type of asthma, and not a direct causal relationship. Further longitudinal studies are clearly needed to clarify this matter,

Table 1. – Studies of the outcome of asthma with objective assessment of airway function

First author [Ref.]	Study design/ inclusion criterion	Subjects	n	Age yrs	Follow-up yrs	Endpoints	Predictors of outcome
McNichol [16-18]	Population-based	Asthma Controls	378 106	7	7 (4)	Symptoms, FEV_1, FEV_1/VC, hyperinflation	Symptoms, age at onset, FEV_1, sex, blood eosinophils
Martin [4, 19]	Population-based	Asthma Controls	378 106	7 (10)	14 (11)	FEV_1, FEV_1/VC, AR, EIB, symptoms	Symptoms, FEV_1/VC
Schachter [15]	Population-based	Asthma Nonasthma	731 230	>7	6	Symptoms, FEV_1, FEV_1 decline	Symptoms, CMH
Giles [20]	Population-based	Asthma	281	7	13	Symptoms, $FEV_{0.5}$	Symptoms
Østergaard [21]	Hospital-based	Asthma Controls	156 104	5–11	3	Hospital admissions, FEV_1 % pred, treatment	Symptoms, nonatopic asthma
Bronnimann [22]	Population-based	Asthma Nonasthma	136 2300	7–79	9.4	Symptoms	FEV_1 % pred, symptoms, age, CMH
Burrows [23]	Population-based/ FEV_1 <65 % pred	Asthma COPD	27* 90	40–74	10	FEV_1 decline	
Nishima [24]	Hospital-based	Asthma	89	7–15	5–9	Symptoms, serum IgE	
Peat [7]	Population-based/ FEV_1 >60 % pred	Asthma Controls	92 186	22–69	18	FEV_1 decline	FEV_1/FVC, (AR)
Jonsson [25]	Hospital-based	Asthma	119	5–15	27	Symptoms	Age at onset, atopy, eczema, hospitalization, infections
Østergaard [26]	Hospital-based	Asthma Nonatopic asthma	72 84	5–12	6	FEV_1, hyperinflation, bronchiectasis	FEV_1 % pred, IgG, eosinophils
Friberg [13]	Hospital-based/ male	Controls Asthma	59 20	8.5–13	14	Symptoms, TLC, FEV_1 % pred	Symptoms
Kelly [10, 27, 28]	Population-based	Asthma Controls	378 160	7 (10)	21 (18)	FEV_1, symptoms, AR	Symptoms, FEV_1/VC
Gerritsen [29, 30]	Hospital-based	Asthma	119	6–14	16	Symptoms, AR, FEV_1 % pred	FEV_1 % pred, AR, symptoms
Sporik [31]	Population-based/ atopic parent	Asthma	67	0	11	Symptoms, atopy, AR	Symptoms
van Schayck [32]	Hospital-based	Asthma	71	>30	2	FEV_1 decline	AR, (atopy)
Almind [33]	Hospital-based	Asthma	343	18–80	7	FEV_1 decline	Age, smoking, CMH
Croner [34]	Population-based/ ever asthma	Asthma	89	0	11.5–14.4	Symptoms, EIB, AR, allergy	
Weiss [8]	Population-based	Asthma Nonasthma	67 535	5–9	13	Change in FEV_1, FVC, and $FEF_{25–75\%}$	Sex, symptoms
Ulrik [35]	Hospital-based	Asthma	180	15–70	10	FEV_1 decline	Age, FEV_1, FEV_1/VC, reversibility, treatment, blood eosinophils
Kokkonen [36]	Hospital-based	Asthma Controls	131 29	<15	>6	Symptoms, FEV_1, AR, FEV_1/FVC change	Symptoms, FEV_1/FVC, treatment, eczema
Roorda [11, 37–39]	Hospital-based	Asthma	408	8–12	14.8	Symptoms, AR, FEV_1 % pred, blood eosinophils, skin tests	Symptoms, AR, FEV_1 % pred, sex, smoking
de Gooijer [40]	Population-based	Asthma Controls	20 40	8–11	27	Symptoms, FEV_1, AR	Atopy, symptoms
Kjellman [41]	Hospital-based	Asthma	58	5–14	15	Symptoms, allergy, FEV_1, medication	Age at onset, lung function, symptoms, reversibility
Jenkins [42]	Population-based	Asthma Controls	1000 1000	7	25	Symptoms	Symptoms, sex, lung function, age at onset, parental asthma
Ulrik [35]	Population-based	Asthma Nonasthma	396 10556	>20	5	FEV_1, decline	Age, new asthma, smoking, CMH
Oswald [43]	Population-based	Asthma Controls	374 106	7 (10)	28 (25)	Symptoms	Symptoms
Godden [44]	Population-based	Asthma Controls	121 167	9–15	25	FEV_1, symptoms, AR	Symptoms, FEV_1 % pred
Boulet [45]	Hospital-based	Asthma	40	20–68	5	FEV_1, AR	Anti-inflammatory treatment, atopy
Ulrik [9, 46]	Hospital-based	Asthma	40	20–68	5	FEV_1, AR	Anti-inflammatory treatment, atopy

Table 1 continued on next page

table 1. – continued

First author [Ref.]	Study design inclusion criteria	Subjects	n	Age yrs	Follow-up yrs	Endpoints	Predictors of outcome
POSTMA [47]	Population-based	Asthma	85	5–15	10.7	Symptoms, FEV1/FVC FEV1 % pred	Symptoms, FEV1 % pred, smoking, age at onset, blood eosinophils
STRACHAN [48]	Population-based	Asthma Controls	1060 275	0	35	FEV1, reversibility, FEV1/FVC, symptoms	Age at onset, symptoms
PANHYUSEN [49]	Hospital-based	Asthma Drop-outs	181 245	13–44	25	Symptoms, AHR	Age, airway obstruction, treatment delay, serum IgE
OSWALD [50]	Population-based	Asthma Controls	374 106	7 (10)	28 (25)	FEV1, FEV1/FVC, symptoms, AR	FEV1 % pred, symptoms
LANGE [51]	Population-based	Asthma Nonasthma	400 17106	20–90	15	FEV1 decline	Symptoms, smoking
GROL [52]	Hospital-based	Asthma	119	6–14	26	FEV1 % pred FEV1 decline	FEV1, AR, eosinophils, atopy

Age (at enrolment) and follow-up data are presented as range or mean. Values in parentheses represent a second group of patients included in the Melbourne study when the first group were 10-yrs-old. FEV1: forced expiratory volume in one second; COPD: chronic obstructive pulmonary disease; VC: vital capacity; AR: airway responsiveness; EIB: exercise-induced bronchoconstriction; $FEV_{0.5}$: forced expiratory volume in 0.5 s; IgE: immunoglobulin E; TLC: total lung capacity; FVC: forced vital capacity; $FEF_{25–75\%}$: forced mid-expiratory flow; AHR: airway hyperresponsiveness; CMH: chronic mucus hypersecretion; IgG: immunoglobulin G. *: considered to have features most characteristic of chronic asthmatic bronchitis.

not least the potential impact of hormones, including replacement hormones, on the outcome of asthma.

Smoking

Passive exposure to cigarette smoke in childhood is a risk factor for wheezy bronchitis, airway hyperresponsiveness, and symptomatic asthma [59]. Active smoking is associated with evidence of mild airway obstruction and slowed growth of lung function in nonasthmatic adolescents [60], and, furthermore, active smoking during adolescence is associated with shortening of the plateau phase of the FEV1 level that generally occurs between 20 and 30 yrs of age [61]. Active smoking is, therefore, likely to have a more deleterious effect on lung growth and senescence in asthmatics than in nonasthmatics. However, in both children and adults, an effect of smoking additional to the effect of asthma on longitudinal changes in lung function has been difficult to demonstrate.

Data from a 10-yr follow-up study of children with asthma [9] showed that active smoking was a predictor of a lower FEV1 % pred in early adulthood in patients with nonatopic asthma. In other follow-up studies of children with asthma [10, 29], the outcome with regard to lung function appeared not to be related to smoking habits. It seems likely that the negative effect of smoking on lung function does not become apparent due to a combination of the short period of smoking (number of pack-yrs) and the relatively small groups of patients studied.

LANGE *et al.* [51] investigated the decline in FEV1 in adults with self-reported asthma based on data from a longitudinal epidemiological study of the general population. The sample was followed for a mean of 15 yrs with up to three measurements of lung function, and a total of 17,506 participants contributed data to the analysis. Statistical modelling showed that the decline in lung function normalized by height was significantly steeper in asthmatics (n=400) compared with nonasthmatics, and, furthermore, smoking contributed significantly to the decline in lung function in both asthmatic and nonasthmatic participants, confirming previous preliminary observations from the same cohort [5]. Other studies looking at the effect of smoking on the decline in lung function in adult asthmatics [7, 35] are likely to have included insufficient numbers of smokers with asthma to draw conclusions about the impact of cigarette smoking on outcome, perhaps because individuals with more susceptible airways, *i.e.* asthmatics, are less likely to take up smoking or quit at an early stage.

Although the evidence is scarce, it is difficult not to assume that active smoking has a negative effect, additional to the effect of asthma, on longitudinal changes in lung function in both children and adults suffering from asthma.

Age at onset of symptoms

Studies of the importance of the age at which asthma begins as a predictor of subsequent disease have produced conflicting results. Several studies have shown that early onset of asthma is associated with a negative outcome [25, 41, 42, 48]; other studies have, however, shown that early onset of symptoms is a predictor of a positive outcome [34, 62], and some studies have found no effect whatsoever of age at onset of symptoms on prognosis [29, 36, 38]. There may be several possible explanations for these apparently contradictory findings.

Most of these studies recruited their subjects at 7 yrs of age or later, and they are therefore susceptible to recall bias, not only because some parents may have forgotten episodes of wheezing in early childhood by the time the children are 7 yrs old, but also because the subjects themselves have forgotten, or even deny, having had respiratory symptoms earlier in life. The latter is clearly illustrated by the observation by JENKINS *et al.* [42] that almost half of the young adults (aged 29–32 yrs), participating in a prospective longitudinal study of respiratory symptoms, gave responses to questions concerning age at

onset of respiratory symptoms that contradicted those of their parents at the beginning of the study (when the participants were 7 yrs old). A number of studies are therefore likely to have underestimated the proportion of children with an early onset of asthma who continue to have active asthma as adults.

In a 10-yr follow-up study of children (mean age at enrolment 10 yrs) with asthma, ULRIK *et al.* [9] observed that increasing age at the onset of respiratory symptoms led to a more favourable prognosis (FEV_1 % pred in early adulthood) in children with nonatopic asthma, whereas no such relation was found in children with atopic asthma. The onset of asthma tends to occur later in young females than in young males [53]; and nonatopic asthma, although much less common than atopic asthma, is far more prevalent in young females. Furthermore, sex differences in the outcome of asthma have previously been reported [4, 8, 29]. The observations concerning the importance of the age at which asthma begins may therefore be confounded by the impact of the type of asthma, the duration and severity of previous asthma, recall bias and sex.

Children with episodes of wheezing during the first few years of life constitute a very heterogeneous group. In a substantial proportion of these children, these episodes of wheezing are likely to be associated with small airway calibre, and they will most probably grow out of their tendency to wheeze [31]. The majority of the remaining children with early onset of episodes of wheezing are children with early expression of asthma, and who are often, as reported by MARTINEZ *et al.* [63], characterized by elevated levels of immunoglobulin (Ig)E and more symptoms during the first year of life than children with only transient early wheezing. At the time of first presentation, children with transient early wheezing are clinically indistinguishable from the children with early expression of asthma, and the degree of admixture of children with transient early wheezing in various studies of the outcome of childhood asthma is, therefore, likely to have substantial impact on the observed relation between age of onset and prognosis.

Based on the available information, it can be concluded that the importance of age at onset should be downplayed, as it is likely not to have an independent effect on outcome, and that the focus instead should be on the overall severity of the asthma at its presentation.

Duration of asthma

Information on the precise duration of asthma is difficult to obtain, but evidence from studies by BURROWS *et al.* [64], ULRIK and LANGE [5], and POSTMA and LEBOWITZ [47] suggest that adult asthmatics may have an excessive annual decline in lung function prior to the time of diagnosis, and also in the first years following the onset of asthma [5, 47]. These findings suggest that the asthmatic processes in the airways may be more pronounced early in the course of the disease and then level off in later-stage persistent asthma, or might reflect the impact of treatment on the inflammatory changes in the airways.

In adult asthmatics, the degree of lung function impairment seems to be related to the duration of previous asthma [65], and evidence from a longitudinal study of adult asthmatics suggests that longer duration of the disease may be associated with increasing decline in lung function [35]. Furthermore, based on data from the National Child Development Study, a large, nationally representative sample of young British adults who were contacted regularly from birth until 34–35 yrs of age, STRACHAN *et al.* [48] reported a highly significant trend in the direction of poorer ventilatory function among subjects with long-standing respiratory symptoms. In line with these findings recent cross-sectional studies of adult asthmatics have observed that incomplete reversibility of airflow obstruction may be found in some, most probably a minority, patients with long-standing disease [66, 67]. These observations suggest that long-standing airway inflammation may lead to, perhaps nonreversible, structural changes in the airway wall.

Both newly diagnosed asthma and long-standing asthma appear to be associated with unfavourable longitudinal changes in lung function, possibly reflecting increased airway vulnerability initially, possibly owing to unopposed inflammation, and progressive airway remodelling due to chronic inflammation.

Severity of symptoms

Studies looking at the impact of severity of symptoms and frequency of symptoms on longitudinal changes in lung function, primarily FEV_1 and FEV_1/forced vital capacity (FVC), have consistently shown that more severe/frequent symptoms are associated with a worse outcome, *i.e.* lower level of lung function at the end of the study period [10, 41, 46, 50].

In the Melbourne study, initiated in 1964, 401 children were randomly selected from 30,000 7-yr-old schoolchildren based on parents′ responses to questions relating to their child′s history of asthma, wheezing episodes and bronchitis [16–18]. The cohort comprised a control group of 106 children, a group of 75 children with mild wheezy bronchitis, a group of 107 children with wheezy bronchitis, and a group of 113 children with asthma. To obtain a larger group with severe asthma, a second sampling was carried out from the same age cohort as the original subjects at 10 yrs of age, and a group of 83 with severe asthma was added to the original cohort [4, 19]. So far, these children have been followed up to 35 yrs of age and have been studied at 7, 10, 14, 21, 28, and 35 yrs of age. It is evident from this excellent longitudinal study that resting airways obstruction, as indicated by low FEV_1/vital capacity (VC) ratio and FEV_1 % pred, becomes more common as wheezing frequency increases [10] and, furthermore, that those subjects with frequent and persistent asthma in childhood continue to have abnormal lung function in mid-adult life [50].

Growth and decline in lung function have clearly been shown to be adversely affected by severe persistent asthma. However, whether the outcome differs between asthma of varying inherent severity but comparable symptom expression owing to the effect of treatment, especially use of anti-inflammatory therapy, and/or poor perception of symptom severity, is presently unknown.

Atopy

Atopy, defined as a positive skin test reactivity to inhalant allergens, is found in the majority of patients,

especially children, with asthma, but the association between atopy and the outcome of asthma is not straightforward. Some studies have pointed to a negative effect [20, 27, 28, 40, 68, 69] and some to no effect [7, 19, 30, 32, 49] of atopy on outcome. In a number of these studies, however, outcome of asthma is defined as the presence or absence and severity of respiratory symptoms, especially those studies reporting a negative effect of atopy on outcome. Only a few long-term longitudinal studies have focused on the possible impact of atopy on longitudinal changes in lung function in patients with asthma.

Evidence from longitudinal population studies indicates that skin test-positivity is associated with an accelerated decline in FEV1 [70, 71]. However, PEAT *et al.* [7] analysed questionnaire and lung function data collected during seven population health surveys over 18 yrs in Australia for 92 subjects with asthma and 186 nonasthmatic subjects. Only subjects with at least four observations were included in the analysis, and the age range at enrolment was 22–69 yrs. Nonsmoking males with asthma had an excess decline in FEV1 of 15 $mL \cdot yr^{-1}$ compared to the normal controls, but there was no association between individual regression slope and atopic status as measured by the total number of positive skin prick tests (r=-0.03). In line with this observation, ROORDA *et al.* [37] reported that allergy in the child did not contribute to the prognosis of asthma from childhood to young adulthood. Furthermore, PANHUYSEN *et al.* [49] reported from a 25-yr follow-up study of a hospital-based cohort of asthmatics that atopy, assessed by skin tests, did not appear to be a significant determinant of outcome. In a 2-yr follow-up study of adult asthmatics, VAN SCHAYCK *et al.* [32] observed no independent effect of atopy on the FEV1 slope.

BOULET *et al.* [45] looked at changes in asthma severity, as reflected by changes in airflow obstruction and airway responsiveness, over a 5-yr period in 40 adults with-mild- to moderate asthma. The mean changes in FEV1 and provocative concentration of histamine causing a 20% fall in FEV1 (PC_{20}) were similar among atopics and nonatopics, whereas there was an increased number of atopics whose airway responsiveness had improved. Based on the first three surveys of a hospital-based cohort of children with asthma (age range 5–14 yrs at inclusion and 32–42 yrs at last follow-up), GROL *et al.* [52] reported that a high number of positive skin tests in early adulthood (age range at second survey 22–32 yrs) was associated with a significantly smaller decline in FEV1 over the following 10 yrs.

ØSTERGAARD [21, 26] and ULRIK *et al.* [46] have reported observations from longitudinal studies of children with asthma that the prognosis with regard to lung function is worse for children with nonatopic asthma than for those with atopic asthma. In a 7-yr follow-up of adult asthmatics, ALMIND *et al.* [33] found no difference in the annual loss of lung function between atopics and nonatopics. The lack of difference between the two groups may, however, reflect the effect of smoking on lung function decline, as 83% of the nonatopic and 71% of the atopic patients were smokers. Another Danish hospital-based follow-up study of adults with asthma showed that the decline in lung function was steeper in nonatopic asthmatics compared to atopic asthmatics [35], even when the age difference between the two groups of patients was taken into account [72]. As in most studies, the patients with nonatopic asthma were older than the patients with atopic asthma, and as lung function decline accelerates with age [5], the observed difference between atopic and nonatopic asthmatics might be, at least partly, explained by the difference in age between the two groups.

Atopy is a known risk factor for symptomatic asthma, and in the nonasthmatic population it may also be a risk factor for an accelerated decline in lung function. However, in both children and adults with established asthma, it appears reasonable to conclude from the above-mentioned studies that atopy is not an independent determinant of prognosis with regard to lung function, suggesting that inflammatory processes in the airways of patients with asthma run their own courses irrespective of the subjects' atopic status.

Level of lung function

Longitudinal population studies have, as mentioned above, consistently shown that asthmatics, on average, have a lower level of lung function at the first survey of the samples compared to the nonasthmatic participants [5, 7, 47], suggesting an accelerated decline in (or slowed growth of) lung function prior to inclusion and/or diagnosis. However, when the initial values differ substantially between the groups of interest, it might be difficult to ascertain that an initial low level of lung function is a risk factor for subsequent excessive decline in lung function.

From the Dutch follow-up study of a large hospital-based cohort of children with asthma, ROORDA *et al.* [11] reported that the only childhood variable predictive of the adult level of FEV1 was the level of FEV1 % pred. In keeping with this, OSWALD *et al.* [50], GROL *et al.* [52], GODDEN *et al.* [44], and ULRIK *et al.* [46] reported from studies of various cohorts of children with asthma that a low level of lung function in childhood was associated with a low level of lung function in early adulthood. This observation might, however, apart from transient bronchospasm, reflect the impact of previous asthma and/or ongoing airway inflammation at the time of the measurements, and not progressive airflow obstruction. Asthmatic children and adolescents seem to exhibit growth of lung function parallel to but at a lower level than in nonasthmatics [10, 11, 46, 50, 52], not least if they remain symptomatic, which does not point to a progressive deterioration in airway function predicted by the initial lower level of lung function.

In nonasthmatic adults, FLETCHER *et al.* [73] have described the "horse racing effect", which is a relation between the level of FEV1 and its rate of decline over time. An inverse relation between initial FEV1 and decline in FEV1 has been found for adults with atopic asthma [35]. Furthermore, subgroup analysis of data from the Copenhagen City Heart Study comparing subjects with persistent asthma and nonasthmatics with comparable levels of FEV1 % pred at enrolment showed that the decline in FEV1 was, on average, 31 $mL \cdot yr^{-1}$ higher in the persistent asthma group [5].

Although the available evidence is limited, it can be concluded that it remains to be established whether or not a low level of lung function is an independent factor for disease progression with regard to lung function changes in asthma. The reported observations on the relationship

between initial lung function and change over time may well be explained by the effect on lung function of ongoing, and previous, clinical asthma.

Airway responsiveness

Airway hyperresponsiveness is regarded as a hallmark of current symptomatic asthma [74], and it may precede the development of asthma in both children and adults [75–77]. Furthermore, in asthmatics, the degree of airway responsiveness is, although imperfectly, related to the severity of symptoms, medication needs, fluctuations in lung function and the number and state of activation of airway inflammatory cells such as eosinophils, lymphocytes and metachromatic cells [78–81]. Not least in asthmatics, increased airway responsiveness is likely to reflect past and/or ongoing airway inflammation. However, an inverse relationship between prechallenge level of lung function and the degree of airway responsiveness has been demonstrated in both children and adults with asthma [47, 82, 83], a relationship also observed in nonasthmatics [84], suggesting that the measured degree of airway responsiveness partly reflects the prechallenge airway calibre. Reported findings from studies where airway responsiveness has been measured at the end and not at the start of the study [7, 35] are therefore difficult to interpret because increased airway responsiveness may be either a cause or a consequence of an accelerated decline in (or slowed growth of) lung function.

Evidence from population studies suggest that airway hyperresponsiveness is a predictor of lower maximally attained levels of FEV1 in early adulthood and associated with an accelerated decline in lung function in adulthood [70]. GERRITSEN *et al.* [29] studied the outcome of childhood asthma, primarily changes in respiratory symptoms, spirometry, and airway responsiveness to histamine, in 101 adults (mean age at enrolment 9.7 yrs and at follow-up 26.4 yrs). Children with a low provocative concentration of histamine causing a 10% fall in FEV1 (PC10) were significantly more likely to have current respiratory symptoms as adults than children with normal levels of responsiveness. In a regression model including the level of FEV1 % pred in childhood, low PC10 values in childhood were found to be significantly related to low FEV1 % pred values in adulthood. In another Dutch follow-up study of children with asthma, ROORDA *et al.* [11] found no association between the childhood degree of airway responsiveness and the adult level of lung function. VAN SCHAYCK *et al.* [32] studied the relationship between airway responsiveness and annual rate of decline in FEV1 in 71 adult patients with asthma over a period of 2 yrs, and reported that airway hyperresponsiveness was related to the FEV1 slope independently of the FEV1 level. As judged by the mean level of lung function, the patients included in the two studies showing a significant association between airway responsiveness and longitudinal change in FEV1 appear to have had more severe asthma than the patients included in the study by ROORDA *et al.* [11], and confounding by severity is therefore a possibility.

Based on the available longitudinal studies of asthmatics including measurements of airway responsiveness at the beginning of the study, it seems, however, likely that airway hyperresponsiveness, at least in patients with moderate-to-severe disease, is associated with both impaired growth of lung function in children and accelerated decline in lung function in adults. The impact of anti-inflammatory treatment on the association between airway responsiveness and annual change in lung function is presently not known, although evidence from a study by BOULET *et al.* [45] might suggest that regular use of inhaled corticosteroids over a 5-yr period may lead to an improvement in both airway responsiveness and FEV1.

Response to bronchodilators

Asthma is characterized by reversible airflow obstruction either spontaneously or following treatment with *e.g.* bronchodilators, but large bronchodilator responses have been suggested as a risk factor for unfavourable changes over time in lung function. VOLLMER *et al.* [85] looked at the relationship between bronchodilator responsiveness and decline in FEV1 in two population-based cohorts (n=795) followed for 9–11 yrs with biennial measurements of lung function (bronchodilator hyperresponsiveness was defined as a >7.72% change from baseline in FEV1). Hyperresponsive subjects had, on average, steeper rates of decline than nonresponsive subjects, irrespective of smoking habits. Reversibility, however, was tested at the end of the follow-up period, and this finding, therefore, was not unexpected owing to the interrelationship between the degree of reversiblity and the prebronchodilator level of FEV1. Prospective studies on bronchodilator responsiveness as a risk factor for accelerated decline in lung function have yielded conflicting results [86–88], some studies have reported steeper declines and some slower declines, probably due to differences in the groups of subjects studied, *e.g.* selection of subjects with pre-established nonasthmatic obstructive pulmonary disease.

KJELLMAN and HESSELMAR [41] reported from their prospective study of a hospital-based cohort of children with asthma that subjects who had <10% reversibility of FEV1 at the first follow-up (after 4 yrs) were more likely to have mild or no asthma, defined on the basis of symptom score, at the end of the study (after 15 yrs) than those children who had a more marked response to a bronchodilator; data on the relationship between reversibility and changes in lung function were not reported.

From a longitudinal study of a representative population sample of adults, POSTMA and LEBOWITZ [47] reported that larger bronchodilator responses were related to steeper declines in FEV1 among subjects with persistent asthma. Furthermore, ULRIK *et al.* [35] observed that a high degree of reversibility at the time of enrolment was associated with a steeper decline in lung function over the following 10 yrs in adults with nonatopic asthma.

The high degree of reversibility in pulmonary function following administration of a bronchodilator, *i.e.* reduced baseline pulmonary function, is a known marker of poorly controlled asthma [89]. This, in combination with the above-mentioned observations, may suggest that a high degree of bronchodilator reversibility is likely to identify asthmatics at risk of a poor outcome with regard to subsequent changes in lung function.

Blood eosinophils

Airway infiltration by eosinophils and T-lymphocytes is recognized as being central to the pathophysiology of asthma [90], and peripheral eosinophilia is found in a large proportion of subjects with current asthma, although the number of eosinophils in peripheral blood is known to decrease with age in asthmatics [17, 30]. However, little is known about the predictive value of blood eosinophilia in relation to the outcome of asthma.

GERRITSEN *et al.* [30] reported that eosinophilia in childhood did not predict the presence of respiratory symptoms in adulthood, whereas another follow-up study of children with asthma found a weak, but statistically significant, correlation between the blood eosinophil count in childhood and symptom score in adulthood [46].

Unpublished data from the latter study suggests that a higher eosinophil count in childhood might be associated with a lower level of FEV1 % pred in early adulthood (fig. 1). Longitudinal studies of adult asthmatics have, at most, revealed a borderline significant association between eosinophil count at enrolment and subsequent decline in FEV1 [35, 47, 52], in one study possibly owing to the effect of treatment with corticosteroids on blood eosinophil count [35].

The peripheral eosinophil count, as well as markers of eosinophil activation in peripheral blood, is related to the severity of current asthma, which may suggest an association between increasing eosinophil activation, *i.e.* severity of airways inflammation, and unfavourable longitudinal changes in lung function in asthmatics. However, the evidence for such an association is at present limited, possibly owing to the impact of corticosteroids on eosinophil inflammation in the airways.

Chronic mucus hypersecretion

Chronic mucus hypersecretion, defined as daily sputum production for $\geq$3 months·yr^{-1} in at least two consecutive years, and nonreversible obstructive ventilatory impairment are common findings in smokers, but may not be causally related [73, 91], although chronic mucus hypersecretion may be related to the outcome of chronic obstructive pulmonary disease (COPD) [91]. Chronic mucus hypersecretion is also found in a substantial proportion of never-smokers with asthma [33, 44]. From a 6-yr follow-up study of a population sample from Connecticut, involving 1,303 Caucasian residents aged $\geq$7 yrs, SCHACHTER *et al.* [15] reported not only a positive association between asthma and chronic mucus hypersecretion, but also an association between worsening asthma during the years of follow-up and the presence of cough and phlegm, which might suggest an association between chronic mucus hypersecretion and the outcome of asthma. This assumption is supported by evidence from at least two population studies. ULRIK and LANGE [5] and LANGE *et al.* [51] observed that chronic mucus hypersecretion in adults with self-reported asthma was significantly related to an increased annual decline in FEV1 compared with the decline in nonsmokers without mucus hypersecretion who reported asthma. Furthermore, POSTMA and LEBOWITZ [47] reported from their longitudinal population study that individuals with chronic mucus hypersecretion combined with asthma had greater declines in FEV1 than those who only had asthma, an association not abolished by adjustment for the initial level of FEV1.

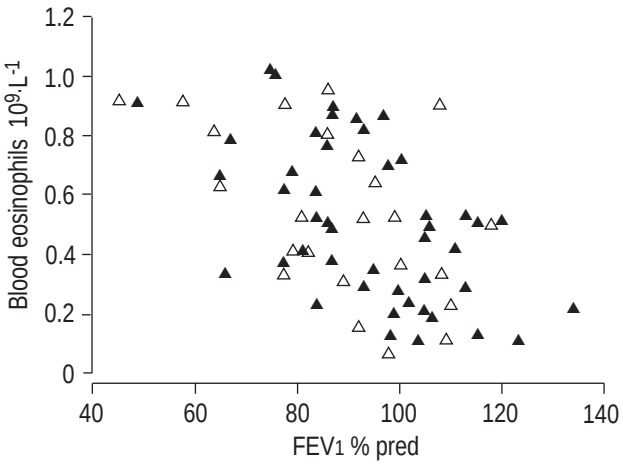

Fig. 1. – Relationship between eosinophil count in childhood and forced expiratory volume in one second (FEV1) % predicted in early adulthood in patients with nonatopic (△) and atopic asthma (▲).

Chronic mucus hypersecretion may be regarded as a marker for poorly controlled airway inflammation, and based on the above mentioned studies it is possible that chronic mucus hypersecretion in asthmatics may be associated with an accelerated decline in lung function.

Therapy

Anti-inflammatory therapy, especially treatment with corticosteroids, (preferably inhaled corticosteroids) can effectively improve the clinical expression of asthma, and, furthermore, inhaled corticosteroids have been shown to reduce the chronic inflammation seen in the airways of asthmatic patients [92]. However, the influence of treatment with corticosteroids on the long-term outcome of asthma is difficult to assess due primarily to changes in treatment regimens over the years and the lack of controlled clinical trials.

Persistent airway inflammation may be assumed to interfere with normal lung growth during childhood and adolescence, thereby leading to lower maximally attained levels of lung function in early adulthood. Minimizing the degree of airway inflammation may therefore, at least theoretically, lead to a more favourable growth of lung function in children with asthma. However, two longitudinal studies of childhood asthma by MARTIN *et al.* [93] and KOKKONEN and LINNA [36] concluded that pharmacotherapy had no influence on outcome of the disease, but it should be noted that <25% of the children included in the studies were treated with inhaled corticosteroids.

In a prospective, open, nonrandomized trial, AGERTOFT and PEDERSEN [94] followed 216 children at 6-month intervals for 1–2 yrs without inhaled budesonide and then for 3–6 yrs on inhaled budesonide, and a further 62 children ("controls") treated with theophylline, β_2-agonists and sodium cromoglycate, but without inhaled steroids, for the same period. An annual decrease in FEV1 % pred of 1–3% was observed in children not treated with budesonide, compared with the children treated with budesonide, although the "controls", on average, experienced a substantial improvement in the level of FEV1 during the

observation period. In contrast, FEV1 improved significantly with time during budesonide treatment, compared with both the run-in period and with the "control group". Furthermore, a significant inverse relationship was found between the duration of asthma at the start of treatment with budesonide and the annual increase in FEV1 during budesonide therapy. After 3 yrs of anti-inflammatory treatment, children who started budesonide therapy >5 yrs after the onset of asthma had significantly lower FEV1 % pred than children who received budesonide within the first 2 yrs after the onset of asthma, although the level of FEV1 in both groups, on average, was within the reference range (96% pred and 101% pred, respectively). The authors concluded that early intervention with inhaled corticosteroids may prevent the development of nonreversible airway obstruction and reduce the risk of undertreatment. However, transient bronchospasm and not nonreversible airflow obstruction might explain the reported effect of duration of asthma prior to the initiation of budesonide therapy, as no attempt was made to reverse the airflow obstruction, and only baseline, *i.e.* prebronchodilator, lung function was measured.

KONIG and SHAFFER [95] reported from a retrospective study of 175 asthmatic children with a mean follow-up time of 8.4 yrs that delay in starting cromoglycate therapy (as add-on to *p.r.n.* bronchodilator) had a negative effect on changes in spirometry, whereas delay in starting inhaled steroids (as add-on to cromoglycate) had no detrimental effect on outcome. Furthermore, a decrease in spirometric values was observed for patients treated with bronchodilators only. The authors concluded that: the critical step is the initiation of anti-inflammatory therapy, anti-inflammatory treatment improves the long-term prognosis in asthma, and administration of nonsteroid anti-inflammatory drugs earlier than presently recommended may further improve the outcome. Given the retrospective, and uncontrolled, design of the study, prospective studies are clearly needed to confirm these findings, not least the observations regarding the effect of cromoglycate therapy. This drug has so far not been shown to suppress the inflammatory reaction in the airways, as judged by specimens such as bronchial biopsies, bronchoalveolar lavage fluid or induced sputum. These two studies do, however, lend support to the hypothesis that (early) intervention with anti-inflammatory therapy may improve the outcome with regard to lung function in children with asthma. In contrast, OSWALD *et al.* [50] reported from the latest follow-up of the cohort of children with asthma from Melbourne that there was no significant difference at 35 yrs of age in FEV1 % pred between the control subjects and those in the mild wheezy bronchitis, wheezy bronchitis, and asthma groups who had not received corticosteroids. Not surprisingly, the level of FEV1 % pred was reduced in subjects in the wheezy bronchitis, asthma, and severe asthma groups who had received corticosteroids, most probably owing to more severe disease and not to an adverse effect of anti-inflammatory treatment. This latter study was not designed to assess the effects of therapy on outcome, but the observations clearly indicate that further knowledge is needed before valid conclusions can be drawn concerning the effect of therapy on outcome of childhood asthma.

The question of a potential beneficial effect of therapy on the outcome of asthma in adults has been addressed in a number of studies, although some of these studies were not designed to investigate the role of therapy prospectively. When re-examined for the second time in adulthood, GROL *et al.* [52] reported from their longitudinal study of children with asthma that treatment with corticosteroids reduced the annual decline in lung function. BOULET *et al.* [45] examined changes in airflow obstruction after a 5-yr period in 40 adults with mild-to-moderate asthma and found that the number of subjects who experienced a significant increase in FEV1 tended to be higher in the group using corticosteroids regularly (>9 months·yr^{-1}), and, furthermore, that the number of subjects with a significant reduction in FEV1 was lower when inhaled corticosteroids were used regularly.

In an uncontrolled trial, SELROOS *et al.* [96] examined the effect of inhaled corticosteroids in patients with varying duration of asthma symptoms before the initiation of therapy. A total of 105 adults with mild-to-moderate asthma were treated with inhaled budesonide for 2 yrs, and the patients were divided into groups according to their duration of symptoms. The greatest rate of improvement in lung function occurred within the first 3 months of budesonide therapy, irrespective of symptom duration; maximum improvement in lung function was seen after 1 yr, with no further increase during the second year of treatment. A significant negative correlation was found between duration of symptoms and maximum increase in lung function. Throughout the study period, the groups of patients with symptoms for <2 yrs at the beginning of the study had significantly higher mean FEV1 values compared with the groups of patients with a symptom duration >5 yrs, but not compared to the group of patients with a symptom duration of 2–5 yrs before the initiation of budesonide therapy. It was concluded that inhaled corticosteroids should be used as the first-line therapy in asthma and should be given soon after diagnosis to have the best possible effect, and, furthermore, that the maintained level of improved lung function over 2 yrs indicates that early treatment with an inhaled corticosteroid may prevent patients from developing nonreversible airflow obstruction. However, due to the uncontrolled design of this study it might be difficult to draw valid conclusions, and, furthermore, transient bronchospasm might have influenced the measurements. HAAHTELA *et al.* [97] studied 103 patients in whom asthma had appeared within the previous year, who were randomly assigned in a blinded fashion to either inhaled budesonide or inhaled terbutaline for 2 yrs. The study showed that early intervention with budesonide was more effective than that with terbutaline at reducing airway hyperresponsiveness, improving peak expiratory flow rate, reducing respiratory symptoms and reducing the need for supplemental β_2-agonist, although the average increase in FEV1 in the budesonide-treated group was only 130 mL. It was concluded that inhaled budesonide is an effective first-line therapy in newly detected asthma. The study was continued for another year [98] and patients who had previously received budesonide were randomized to either low-dose budesonide or placebo, and the previously terbutaline-treated group received open-label budesonide. The effects obtained by treatment with budesonide were maintained at the lower dose, whereas most patients who received placebo experienced a decline in lung function and an increase in airway responsiveness. After 1 yr of budesonide treatment, the patients who were switched from terbutaline to budesonide experienced worse lung

function than patients who re-ceived budesonide for the entire duration of the study. The authors concluded that early treatment with budesonide results in long-lasting control of asthma, and that discontinuation of anti-inflammatory treatment often result in exacerbation of the disease. Comparable findings have been reported by WAALKENS *et al.* [99] from a study of a smaller group of teenagers with asthma, who were randomized either to continue inhaled steroids or to tapering-off followed by placebo. Cessation of inhaled corticosteroids resulted in an increase in symptoms, supplemental use of bronchodilator and airway responsiveness and a decrease in lung function. The findings of the latter two studies point to the conclusion that inhaled corticosteroids can suppress the expression of asthma, but cannot cure the disease.

Based on the above-mentioned studies, not least the controlled trial by HAAHTELA *et al.* [97, 98], it is tempting to conclude that early intervention with adequate anti-inflammatory therapy, primarily with inhaled corticosteroids, can positively alter the long-term outcome of asthma. However, positive changes in lung function, and other markers of asthma severity, observed after 1–5 yrs of treatment may not reflect long-term changes in the progression of the disease. Furthermore, asthma is a very variable disease, and most patients are probably diagnosed at a time when their asthma is worse than its inherent average severity and the potential for improvement is therefore at its greatest. A very good initial response to relevant, *i.e.* anti-inflammatory, therapy should therefore be anticipated, but may not necessarily be related to a better prognosis.

The available evidence indicates that institution of anti-inflammatory therapy early in the course of asthma, especially in children, is likely to improve the "short-term" changes in lung function, but long-term controlled studies are needed to verify whether or not anti-inflammatory therapy can positively influence the natural history of asthma, *e.g.* the outcome of asthma after ≥20 yrs.

Persistence and type of airway inflammation in severe asthmatics

Recent evidence suggests that treatment with inhaled corticosteroids, although associated with substantial improvements in lung function and symptoms of asthma, may not be associated with large reductions in markers of airway inflammation in induced sputum samples [100]. Furthermore, some compliant patients with more severe asthma deteriorate clinically in spite of intense treatment with corticosteroids, which may suggest that these patients represent a distinct subgroup within the asthma syndrome spectrum. As mentioned previously, eosinophils are a striking feature of the inflammatory infiltrate seen in bronchial biopsies from asthmatics, and the eosinophil is likely to be the principal effector cell in the pathophysiology of asthma. However, evidence from a recent study by WENZEL *et al.* [101] suggests that airway inflammation persists in severe symptomatic asthmatics in spite of high-dose corticosteroid therapy, and, moreover, that the severe asthmatics had a two-fold higher concentration of neutrophils in bronchoalveolar lavage fluid than both the normal controls and the patients with mild-to-moderate asthma. Furthermore, comparable proportions of neutrophils have been found in induced sputum from stable asthmatics and smokers with bronchitis [102]. In acute exacerbations of asthma, PIZZICHINI *et al.* [103] observed a predominance of eosinophils in induced sputum, whereas FAHY *et al.* [104] found that neutrophils comprised ≥75% of the sputum cells in 56% of the patients who were seen at an emergency department. The latter finding might suggest inclusion of a substantial number of patients with bacterial infection, but this has later been refuted by LAMBLIN *et al.* [105], who reported that neutrophilia in bronchial lavage fluid was not related to concomitant bacterial infection in patients in status asthmaticus. The latter is further supported by studies showing neutrophil recruitment in children with virus-induced asthma exacerbations [106]. SUR *et al.* [107] have, based on *post-mortem* examination of cases of fatal asthma, suggested that sudden-onset fatal asthma is immunohistologically distinct from slow-onset fatal asthma characterized by few eosinophils and a relative excess of neutrophils in the airway submucosa, which raises the possibility that the mechanism of airway inflammation as well as that of airway narrowing in sudden-onset fatal asthma may be quite distinct from those in slow-onset fatal asthma. These findings might suggest a distinct disease entity, most probably primarily found in patients with more severe asthma, characterized by a relative predominance of "neutrophil inflammation" instead of "eosinophil inflammation". It is conceivable that intense treatment with corticosteroids could substantially inhibit the T-lymphocyte/eosinophil driven processes in the airways, and thereby upregulate neutrophil-mediated processes. However, even if these changes in the inflammatory reaction in the airways are partly caused by treatment with corticosteroids, these observations may have important therapeutic and prognostic implications. It is well-known that patients with cystic fibrosis have substantial ongoing neutrophil inflammation in the airways, even if they have clinically mild lung disease, which eventually leads to progressive lung destruction and death [108]. In asthmatics, therapy directed at this "neutrophil inflammation" might prevent or postpone permanent damage to the lungs, and by that means improve the prognosis in those severe asthmatic patients who are most likely to be at the greatest risk of disease progression and preterm death. However, further studies are clearly needed in order to determine the role of the neutrophil leukocyte in the pathogenesis and disease progression of asthma.

Disease progression to nonreversible airflow obstruction and emphysema?

Asthma is by definition a disease with reversible airflow obstruction, but, in recent years, as the inflammatory nature of asthma has been increasingly appreciated, several researchers have suggested that asthma could lead to chronic, nonreversible airflow obstruction.

BROWN and coworkers [65, 109] have studied 89 adults with long-standing asthma and no evidence of other disease likely to cause nonreversible airflow obstruction; diffusion capacity was normal in all patients. Patients with an FEV_1 <85% pred after 2 weeks' treatment with theophylline and β-agonists were given a 2-week course of oral prednisolone. The mean best FEV_1 during the study was significantly lower than the predicted normal value, and inversely correlated to age, duration, and severity of asthma. The authors concluded that asthma alone can cause

nonreversible airflow obstruction and that the degree of obstruction is a function of the duration and severity of previous asthma. It is, however, a possibility that a longer course of corticosteroid therapy could have further improved these patients' lung function. Comparable findings have been reported by BRAMAN *et al.* [110] and CONNOLLY *et al.* [111]. Recent cross-sectional and/or retrospective studies [59, 65, 112] have confirmed that a smaller number of patients with, in most cases, long-standing asthma demonstrate nonreversible airways obstruction in two of the studies [65, 66] despite long-term treatment with systemic and inhaled corticosteroids.

The possible disease progression to nonreversible airflow obstruction has also been studied longitudinally in hospital-based cohorts of adult asthmatics. From a 25-yr follow-up study of 189 adults with asthma, PANHYUSEN *et al.* [113] reported that 14% of the patients had developed nonreversible airflow obstruction, defined as FEV1 <80% pred and change in FEV1 % pred after salbutamol <9%, at the time of follow-up. Furthermore, those patients, who developed nonreversible airflow obstruction, had a faster decline in FEV1 % pred than the remaining group of patients. Comparable results, using the same definition, have been obtained by ULRIK and BACKER [114] from a 10-yr follow-up study of 92 lifelong nonsmoking adults with asthma, as 23% of the patients fulfilled the criteria for nonreversible airflow obstruction.

In conclusion, some patients, most probably a minority, with more severe asthma seem eventually to develop nonreversible airflow obstruction, which in a few cases may result in life-threatening lung function impairment [115]. This may be due to a combination of at least three factors: 1) lower maximally attained level of lung function in early adulthood; 2) excessive decline of lung function throughout adulthood; and 3) airway remodelling caused by long-standing poorly controlled airway inflammation. Treatment regimens for asthma have changed dramatically within recent decades, primarily through the widespread introduction of inhaled corticosteroids. Therefore, the poor outcome of the disease that is presently observed in some patients may be the consequences of earlier less efficient treatment regimens. Future long-term studies of the outcome of asthma in patients who have been treated according to the current international guidelines will hopefully provide an answer to that question.

Pulmonary emphysema is a pathological diagnosis, and surrogate markers, such as diffusion capacity and high-resolution computed tomography (HRCT) scan, are therefore used for *in vivo* diagnosis. The possible disease progression to emphysema in asthmatics is controversial, although suggested >40 yrs ago [116]. PANHYUSEN *et al.* [113] reported from their 25-yr follow-up study of adult asthmatics that 22% of the patients had a postbronchodilator diffusion constant (lung carbon monoxide transfer factor ($T_{L,CO}$)/alveolar volume (V_A)) <80% pred, which was interpreted as suggesting the development of emphysema. However, most of these patients had a significant smoking history, which might offer an alternative explanation for the development of reduced diffusion capacity. The Danish follow-up study of lifelong nonsmoking adult asthmatics [114] revealed no significant differences in mean values for total diffusion capacity, diffusion constant, residual volume or total lung capacity between patients with and without evidence of nonreversible airflow obstruction. BIERNACKI *et al.* [117] performed HRCT scans in lifelong nonsmokers with nonatopic asthma, patients with COPD, and normal controls. Although the patients with COPD had a lower lung computed tomography CT density than asthmatic subjects, both asthmatics and COPD patients had a lower lung (CT) density than the normal controls, and, furthermore, there was a considerable overlap between CT lung density in patients with asthma and COPD. There was no significant correlation between CT lung density and FEV1 and diffusion constant in either of the groups. Other studies using HRCT scans have also reported emphysema-like images in a small proportion of asthmatics [118–120]. Low CT lung density may, however, result from air trapping, and it may therefore be difficult to differentiate between this and true emphysema in asthmatics. Measurements of diffusion capacity might be used to differentiate between air trapping and emphysema, as previously suggested [121], although it should be noted that total diffusion capacity measured by the single breath technique is partly based on an estimate of the V_A obtained by single breath helium dilution. Total diffusion capacity has been shown to correlate with pathological changes and CT lung density in COPD patients with emphysema [122, 123], but these correlations have not yet been shown in asthmatics.

The combination of the available evidence obtained by measurements of diffusion capacity and HRCT scans may suggest that emphysema-like changes may be present in a small number of nonsmoking patients with asthma, but further studies, including comparisons of CT scan results and pathological findings, are needed before valid conclusions can be drawn.

Conclusions

Although the available evidence is limited, the following key conclusions concerning the longitudinal changes in lung function in patients with asthma seem appropriate. 1) The prognosis with regard to changes over time in lung function is good for the majority of patients with asthma. 2) Asthmatics are likely to be more susceptible than non-asthmatics to the deleterious effects of smoking on lung function. 3) Some patients with asthma, especially those with more severe, persistent disease, are at risk of impaired growth of lung function in childhood and excessive decline

Table 2. – Factors important for the outcome of asthma, *i.e.* longitudinal changes in lung function

Early onset of asthma	-
Female sex	↓
More severe symptoms	↓ ↓ ↓
Newly diagnosed asthma	↓
Long-standing asthma	↓ ↓
Smoking	↓ ↓
Airway hyperresponsiveness	↓
Blood eosinophilia	↓
Substantial β_2-reversibility	↓
Atopy	-
Low level of FEV1	↓
Chronic mucus hypersecretion	↓
Anti-inflammatory therapy	↑ ↑

FEV1: forced expiratory volume in one second; ↓: possible decrease; ↓ ↓: probable decrease; ↓ ↓ ↓: highly probable decrease; ↑ ↑: probable increase; –: no effect.

in lung function in adulthood, which may lead to life-threatening lung function impairment. 4) More severe symptoms, persistent airway hyperresponsiveness, eosinophilia, a low level of forced expiratory volume in one second, substantial bronchodilator reversibility and chronic mucus hypersecretion appear to have a negative impact on the longitudinal changes in lung function (table 2). 5) Disease progression to nonreversible airflow obstruction may be observed in a minority of patients with asthma. 6) Early intervention with anti-inflammatory therapy, primarily inhaled corticosteroids, may positively influence disease progression in asthma.

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