Asthma from childhood to adulthood

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Summary, conclusions and general discussion

Documentation of the natural history of childhood asthma is necessary for understanding the disease, for counseling parents and children with asthma and assessing treatment. Studies on the natural history of asthma are limited. Most studies on asthma have been either cross-sectional in nature, or have followed a cohort of asthmatics for a relatively short duration. In studies that start at an adult age, it is difficult to separate subjects with asthma from those with chronic obstructive pulmonary disease (COPD). Therefore, the results of these studies could be a constitute of mixed messages resulting from subjects with asthma and COPD. There is another reason why studies which start in childhood may give different results than studies which start in adulthood. Studies on childhood asthma have shown that about 50 % of the children with asthma outgrow their disease during puberty as assessed by symptoms (1-3). Thus, only a part of the population of children with asthma are seen by an adult lung specialist. This could imply that the population with asthma seen by a pediatrician is phenotypically different from the adult asthmatic population.

The subject of this thesis is a long-term follow-up study over 30 years, starting in childhood. Initially, and during repeated follow-up visits, we performed objective measurements and asked questions about several important issues like medication use. We investigated which factors at the start of the study were associated with the outcome of asthma. One of the characteristics of asthma is an increased bronchial responsiveness to a variety of inhaled stimuli, like cigarette smoke and cold air. This increased responsiveness can be objectivated by measuring the responsiveness of the airways to e.g. histamine, methacholine or adenosine 5'- monophosphate. Primary outcome parameters of our study were bronchial responsiveness as measured by PC_{10} histamine, lung function as measured by FEV_1 and the presence or absence of current symptoms.

Recent studies have shown that subjects with bronchial hyperresponsiveness and subjects with asthma have a greater decline in lung function than those without bronchial hyper-responsiveness and asthma (4-7), suggesting that every effort should be made to reduce bronchial hyperresponsiveness and to prevent asthma or to give an optimal treatment intervention. There is also evidence that subjects with asthma have an increased risk of mortality, compared to subjects without asthma (7,8).

All consensus reports focus on the knowledge that inflammatory processes underlie the clinical expression of asthma, and advocate anti-inflammatory treatment like inhaled corticosteroids as the first line therapy when symptoms occur at least once a week. Inhaled corticosteroids have beneficial effects not only in terms of symptoms, but also in terms of lung function, bronchial responsiveness, diurnal peak expiratory flow (PEF) variability and long-term outcome of asthma (9-12). Despite the high prevalence of asthma and the knowledge about its pathophysiology, the optimal treatment strategy for the individual asthmatic subject is not yet known. With the introduction of long-acting β_2-agonists and a more potent inhaled corticosteroid, new therapeutic strategies became

available. We evaluated the effect and safety of a new inhaled corticosteroid, fluticasone propionate on several outcome parameters of asthma in children. In a long-term study we evaluated the role of salmeterol, a new long-acting β_2 agonist, in the treatment of children with mild to moderately severe asthma.

In **Chapter 1** a general introduction, the background and the aims of the studies are given. The lack of a clear definition of asthma has impeded studies on this disease. Many attempts have been made to develop a definition of asthma useful both in the clinical setting and in population studies. This lack of definition makes it difficult to study the prognosis of asthma from childhood to adulthood.

To investigate which factors may be associated with the progression or remission of asthma, a review of published studies on the outcome of asthma, is given in **Chapter 2**. The effect of age at onset of symptoms, severity of symptoms, allergy, bronchial responsiveness, lung function, viral infections, eczema, gender, active and passive smoking and therapy on the long-term outcome of asthma are being discussed.

From the factors mentioned above, bronchial responsiveness is an important risk factor for both the development and outcome of asthma (13-19). Asthma is a chronic inflammatory process of the airways, and bronchial responsiveness is thought to indirectly reflect this inflammatory process. Bronchial responsiveness has been associated with an increase in symptomatology and need for asthma medication, and a lower pulmonary function. Therefore, we investigated in **Chapter 3** which childhood and early adulthood risk factors are associated with the persistence of bronchial responsiveness into adulthood, and which childhood factors are related to either improvement or worsening in bronchial responsiveness from childhood to adulthood. We also wanted to determine which cross-sectional factors are associated with the severity of bronchial responsiveness at age 32-42 year.

In a 30-year follow-up study, 119 allergic asthmatic subjects were measured 3 times, at age 5-14 yr (visit 1), 22-32 yr (visit 2) and 32-42 yr (visit 3). Different lung function tests, blood tests and allergy tests were measured, a questionnaire was used and physical examination was performed. A better lung function, assessed by FEV_1 in childhood was associated with less severe bronchial responsiveness at age 32-42, independent of other potential risk factors. Larger increases in lung function (FEV_1 values) both from childhood to early adulthood and from early adulthood to age 32-42, a longer time interval from the first to the third measurement and having pets in childhood were associated with less severe bronchial responsiveness at age 32-42. The same factors were found to be associated with less deterioration of bronchial responsiveness from visit 2 to 3. In our study we found an increase in bronchial responsiveness over time in both smokers and ex-smokers. Because smokers have a higher level of IgE (20,21), we separately analyzed the effect of IgE in non-smokers, ex-smokers and smokers. In non-smokers, a higher IgE level at visit 2 (22-32 yr) was a risk factor for more severe bronchial responsiveness at age 32-42.

When we determined cross-sectionally which factors at age 32-42 yr were associated with the severity of bronchial responsiveness at that age, a low level of lung function and

presence of asthma symptoms were associated with more severe bronchial responsiveness, while older age and having pets were associated with less severe bronchial responsiveness. IgE was related to more severe bronchial responsiveness only in non-smokers.
We conclude that a lower lung function in childhood, and less improvement in lung function over time and a high level of IgE in non-smokers were associated with more severe bronchial responsiveness in adulthood.

Another important factor associated with the outcome of asthma is lung function as assessed by FEV_1. Symptom severity, like wheezing and dyspnea are related to pulmonary function (25,26). It is therefore important to know which factors in early adulthood are associated with the level of FEV_1 and which factors are associated with an accelerated decline in FEV_1 throughout adulthood. In **Chapter 4** risk factors for growth and decline of lung function over a period of 30-year were assessed in the same group of asthmatics as mentioned in Chapter 3. A low level of lung function and more severe hyperresponsiveness in childhood were shown to be independent risk factors for a low level of FEV_1 in early adulthood at age 22-32 year. A smaller FEV_1 decline after age 22-32 occurred in those asthmatics who stopped smoking and who continued to use inhaled corticosteroids. Our data stress the importance to study intervention strategies in young childhood and early adulthood to prevent or to postpone further lung function deficit.
Asthma is a very common disease, for which there is still no cure. It is important to know which factors contribute to the best attainable outcome of the disease. In **Chapter 5** we investigated which factors in childhood and early adulthood are associated with remission of asthma over a period of 30-year. In our study we defined remission of asthma as the absence of bronchial hyperresponsiveness, having a good lung function, expressed as FEV_1 >90% predicted, absence of wheeze and asthma attacks and no need for inhaled corticosteroids. We also investigated which co-variables are associated with the separate components that constitute our definition of remission of asthma. We found that 22% of our study group had asthma remission at age 32-42. A better lung function early in life and a higher increase in lung function from age 5-14 to 22-32 were significantly associated with this remission of asthma. Being female was borderline significantly associated with absence of asthma at age 32-42. Almost 50 % of the group of subjects who did still have asthma at age 32-42 did not report symptoms of wheeze and/or asthma attacks, while they still had bronchial hyperresponsiveness, or a low lung function, or used inhaled corticosteroids or had a combination of these three.
If we diagnosed remission of asthma only on the absence of symptoms, we would get a higher percentage of asthma remission, 71 % instead of 22 %. Using absence of symptoms as definition for outgrowing asthma will miss subjects with ongoing airway inflammation based on objective measurements.
For the separate components, we found that a higher level of lung function at visit 1 was significantly associated with a good lung function at age 32-42 yr., and with no need for

inhaled corticosteroids at age 32-42. A higher increase in lung function from age 5-14 to age 32-42 was significantly associated with absence of symptoms at age 32-42 yr., and with a good lung function at age 32-42 yr. The absence of hyperresponsiveness at visit 2, and a low level of serum total IgE at visit 2 are significantly associated with the absence of hyperresponsiveness at age 32-42. We concluded that the outcome of asthma is strongly related to its definition, i.e. different results are shown when outcome of asthma is defined as absence of symptoms or when it is defined as having a good lung function or absence of bronchial hyperresponsiveness or a combination of these components. Only a part of symptomatic asthmatic children will outgrow their disease, as assessed by objective measurements at age 32-42, and that a better lung function early in life and a higher increase in lung function from age 5-14 to 22-32 is associated with this absence of asthma.

Despite the high prevalence of asthma and the recent knowledge about its pathophysiology, the optimal treatment strategy for asthma is yet unknown, especially with regard to the long-term outcome of the disease. The first choice in asthma management is anti-inflammatory medication, such as inhaled corticosteroids, combined with on demand short-acting β_2-agonists for symptom relief. With the introduction of more potent inhaled corticosteroids and long-acting β_2-agonists, new therapeutic strategies became available. In **Chapter 6** we have described effects and side-effects of treatment with a recently developed inhaled corticosteroid, fluticasone propionate, in 34 children with stable moderately severe asthma, in a double blind placebo-controlled trial. After a run-in period of 2 weeks and a treatment period of 3 months there was a follow-up period of 4 weeks during which only bronchodilators were allowed. At home, symptoms of asthma, the use of β_2-agonists and peak expiratory flow (PEF) values were noted in a diary two times a day. Lung function, bronchial hyperresponsiveness (PC_{20}-histamine) and reversibility to β_2-agonists were determined each month. We found that wheezing improved and all PEF values increased during treatment with fluticasone propionate. Lung function as assessed by FEV_1 and bronchial responsiveness improved, and reversibility with 800 μg salbutamol decreased in the fluticasone propionate group. All observed changes were significant, with exception of the change in nocturnal PEF. The effect of fluticasone propionate on symptoms and lung function were transient, since all parameters had returned to pre-treatment values four weeks after cessation of fluticasone propionate. Side effects of fluticasone propionate on the hypothalamus-pituitary-adrenal axis (HPA-axis) were measured by serum and urinary cortisol concentration under fasting conditions. The serum cortisol level did not change during treatment, the urinary cortisol level significantly decreased in the fluticasone propionate group. The latter was, however, only significant when the decrease was compared with an unexplained increase in the placebo group. We conclude that fluticasone propionate 100 μg b.i.d. is effective in children with moderately severe, stable asthma. With respect to side effects, additional studies are necessary to exclude suppression of the HPA-axis during treatment with fluticasone propionate 100 μg b.i.d.

Studies in adults have shown that addition of salmeterol to a moderate dose of inhaled corticosteroid results in a better symptom control and higher PEF values, compared with a doubling dose of the inhaled corticosteroid (27,28). The place of this long-acting β_2-agonists in the treatment of asthma in children is not known and should be further elucidated. In **Chapter 7** we describe the results of a multicenter study in which the addition of salmeterol (50 μg b.i.d.) to a moderate dose of an inhaled corticosteroid (beclomethasone 200 μg b.i.d.) was compared to doubling the dose of an inhaled steroid (beclomethasone 400 μg b.i.d.) and to the initial inhaled corticosteroid (beclomethasone 200 μg dose). In a double-blind placebo controlled parallel study, 177 children with mild to moderately severe asthma participated. After one year of treatment no significant differences between the three treatment groups were found for pre- and post-bronchodilator lung function as assessed by FEV_1 and bronchial responsiveness as assessed by PD_{20} methacholine. However, significant improvements from baseline values were found for FEV_1 and PD_{20} methacholine in all three groups. For morning and evening peak flow values, there was a slight advantage in the group who used salmeterol and inhaled corticosteroids in a moderate dose compared to the group which used inhaled corticosteroids at a moderate dose only, especially during the first months of the treatment period. No significant differences were found between groups for symptom scores, use of additional salbutamol and exacerbation rates (13 courses of prednisolone to 10 patients in the beclomethasone 400 μg +salmeterol group, 8 courses to 7 patients in the beclomethasone 800 μg, and 13 courses to 10 patients in the beclomethasone 400 μg treated group). Growth was significantly more retarded in the group which used a double dose of inhaled corticosteroids. Compliance was high in all treatment groups, where nearly 90% of prescribed medication was used. We conclude that adding salmeterol or doubling the dose of beclomethasone had no additional benefit to 200 μg beclometasone b.i.d. in this selected group of children with moderately severe asthma, in which the compliance with medication was excellent.