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Development and outcome of asthma

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Summary

There can be two phases identified in the natural history of asthma: the development of asthma and the progression of asthma. The outcome of childhood asthma is generally thought to be a good one. However, studies have shown that asthma patients may end up with either severe disease or without disease. These disease states represent the extremes of the disease, i.e. irreversible airway obstruction accompanied by an accelerated decline in FEV₁ as a result of airway remodelling, and complete remission in adulthood without symptoms or need for asthma treatment, a normal lung function and absence of bronchial hyperresponsiveness (BHR). In this thesis these aspects of the natural history of asthma are being described and early life factors associated with either a benign or a poor outcome have been identified.

Chapter 1 gives an introduction on the subject. An increasing number of people is developing asthma compared to the number 30 years ago¹⁻³. This rise in prevalence in recent decades is especially high in the more affluent countries. Recent research has indicated that factors such as exposure to other children⁴⁻⁶ or living on a farm during the first years of life⁷⁻¹⁰ protect against the development of asthma. This finding made scientists focus on the developing immune system to explain the rise in asthma prevalence. The current opinion is that young children and toddlers in the Western society are less exposed in recent decades to factors that induce a Th₁ response from the immune system. This then gives way to the development of a Th₂ response, which is involved in IgE mediated allergy. This decrease in exposure is thought to result from higher hygienic standards and a reduced size of families with less cross-infection between siblings⁵. Recent studies have indicated that there certainly is evidence in favour of this so-called hygiene-hypothesis, but other factors such as family history and pre- and perinatal factors, are also important. In the literature on risk factors for the development of asthma, there is a lack of long-term studies that simultaneously take into account perinatal factors, genetic predisposition, and risk factors later in life such as smoking habits.

After the diagnosis of asthma is made in an individual it is important to know the prognosis of the disease. It is of great priority to determine prognostic factors in childhood asthma since this can lead to more effective and efficient treatment regimens. Several studies have shown that the severity of the disease in childhood, as assessed by presence or severity of symptoms, level of lung function or BHR, is a very important predictor for the severity of the disease in adulthood¹¹⁻¹⁸. The literature concerning early predictive factors for the prognosis of asthma has mainly focused on identification of predictive factors for a symptomatic state of asthma and for the use of anti-inflammatory medication after a certain length of follow-up. Long-term studies on early predictive factors associated with the natural course of other aspects of asthma such as (reversibility of) lung function and BHR, are scarce.

The development of asthma between 1975 and 1995 in Groningen, The Netherlands, the uniqueness of these data, and the availability of detailed data offered us the possibility to study a young adult age group with a predisposition.

In **Chapter 2** risk factors for young adult age were reported at least once than males. Taking into account associated with a reduced dyspnoea) and with those who smoked during childhood associated with a low level of symptoms. Having a low level of lung function associated with both gestational age, maternal smoke exposure) was achieved level of lung

Predictive factors for **3**. Apart from the risk factors the child were also in forceps, or a caesarean medication, and possibly had BHR and almost duration longer than having had a severe the development of and current smoking, exposed to smoke, decreased risk for t There was no association been breastfed for first born, mode of

Chapters 4 to 7 concern worsening of asthma factors that are pre

The development of asthma in a prospective cohort of all newborn babies born between 1975 and 1978 in the Department of Obstetrics of the University Hospital in Groningen, The Netherlands¹⁹, is the subject of chapters 2 and 3 of this thesis. The uniqueness of these studies lies in the long period of follow-up (20 years) and the availability of detailed information on child delivery and other perinatal factors. This offered us the possibility to investigate their association with respiratory morbidity at a young adult age, while at the same time adjusting for smoking habits and familial predisposition.

In **Chapter 2** risk factors for symptom development and level of lung function at a young adult age were investigated. At follow-up 39% of the 1568 responders reported at least one respiratory symptom. Females reported symptoms more often than males. Taking other potential risk factors into account, being first-born was associated with a reduced risk of asthmatic symptoms (wheeze or nocturnal dyspnoea) and with a higher achieved level of lung function. Having had a mother who smoked during pregnancy and having a low birth weight were independently associated with a lower level of lung function but not with the development of symptoms. Having had a severe respiratory tract infection in the first year of life was associated with both the development of asthmatic symptoms and a lower achieved level of lung function at a young adult age. Other investigated perinatal factors (i.e. gestational age, maternal age, method of feeding, and environmental tobacco smoke exposure) were not associated with the development of symptoms or the achieved level of lung function.

Predictive factors for the development of atopy and BHR were identified in **Chapter 3**. Apart from the risk factors described in chapter 2, factors related to the delivery of the child were also investigated, such as mode of delivery (use of vacuum pump, forceps, or a caesarean section), duration of delivery, induction of labour with medication, and position of the foetus. Twenty-five percent of this large birth cohort had BHR and almost 50% had atopy after a follow-up of 20 years. A delivery-duration longer than 12 hours was associated with the development of atopy and having had a severe respiratory infection in the first year of life was associated with the development of BHR. In the non-atopic subjects, being born by induced labour and current smoking were risk factors for the presence of BHR. Finally, having been exposed to smoke prenatally and to pets in childhood were associated with a decreased risk for the development of atopy, especially in BHR-positive subjects. There was no association between the development of BHR or atopy and having been breastfed for at least 2 weeks, having a parent with asthma or allergy, being first born, mode of delivery, position of the foetus during delivery, and birth weight.

Chapters 4 to 7 concern the prognosis of asthma: in chapters 4 and 5 risk factors for worsening of asthma have been described and in chapters 6 and 7 we identified factors that are predictive of remission of the disease in adulthood.

Although asthma is generally believed to be a benign disease with fully reversible airway obstruction, it has recently been acknowledged that a subgroup of patients develops persistent and progressive airway obstruction, probably as a result of airway remodeling. The results of the follow-up study with a duration of 26 years, presented in **Chapter 4**, indicated that the development of irreversible airway obstruction in adulthood (age 35-74) was associated with a lower FEV₁, less reversibility of airway obstruction, and, surprisingly, with less severe BHR at initial testing. The use of anti-inflammatory medication did not result in less airway obstruction but prevented the development of irreversibility. Furthermore, additional analyses suggested that the longer the period between the onset of symptoms and the start of treatment the higher the risk of developing irreversible airway obstruction. Another outcome measure investigated in this chapter was a reduced transfer factor (K_{CO}), a marker that is highly correlated with the presence of emphysema. Having smoked more pack years and being female were independent risk factors for the presence of a reduced K_{CO}. It was concluded that although a reduced K_{CO} and irreversibility are both characteristics of chronic obstructive pulmonary disease, they represent two distinct groups with regard to symptomatology, aetiology, and treatment approach in this population of patients with asthma.

In **Chapter 5** the annual decline of lung function after age 30 in this same cohort was investigated. Only in males who had smoked less than 5 pack years at follow-up did the use of inhaled corticosteroids result in a reduction of the annual lung function decline. This may suggest a different effect of anti-inflammatory medication in men and women and clearly needs further study. Less severe BHR at initial testing and the presence of dyspnoea or wheezing at follow-up were associated with a more accelerated annual decline in lung function in females. The presence of sputum production at follow-up was associated with a more accelerated decline in both sexes. This accelerated lung function decline in the presence of respiratory symptoms possibly indicates undertreatment.

Remission of asthma in adulthood is usually defined as absence of symptoms and no medication use. In chapter 6 and 7 more rigorous definitions of asthma remission were used and early factors associated with remission of asthma were identified.

Chapter 6 describes remission of asthma in the same cohort as used in chapter 4 and 5 to assess a negative outcome of asthma. When remission of asthma was defined as no BHR, FEV₁ > 90% predicted, and the absence of pulmonary symptoms reported by the patient, only 20 subjects (11%) were no longer considered asthmatic when retested after 25 year, while 40% was symptom-free, 21% no longer showed BHR, and 25% had an FEV₁ > 90% predicted. The normalization lung function, as well as remission of BHR and asthma was associated with a younger age and less severe airway obstruction at first testing. A shorter period between the onset of symptoms and the start of specialized treatment was associated with the absence of BHR at follow-up indicating that earlier

treatment of asthma in adolescents and adults.

In **Chapter 7** factors associated with remission of asthma were identified in a cohort of patients who had achieved full remission of asthma after use of inhaled corticosteroids. Patients with BHR (PC₁₀ > 16 mg) and no use of inhaled corticosteroids (age 42 years) 22% was in remission. Fifty-seven percent of patients had normal lung function. Both full and partial remission was associated with a higher level in childhood asthma.

Discussion

Epidemiological and clinical studies

All studies reported in this chapter are epidemiological studies in a population and based on a long-term follow-up over a period of 25 years. Advantages of this design are the selection and the possibility to describe a time sequence of events. Moreover, since childhood asthma recall bias is not present, the relatively high loss to follow-up during the course of the study and progression may be considered as factors that were not

In all studies, except in chapter 2, 3, 4, and 5, after the initial measurement of lung function, a multivariable regression analysis of the initial measurements was performed to adjust for predictors of interest. In chapter 6, adjustment for possible confounding factors was performed. In chapter 7, logistic regression was used to adjust for confounding factors. The outcome category was remission of asthma. The aim was to stratify the a

treatment of asthma may have prevented persistence of the disease, even in adolescents and adults 13 to 44 years of age.

In **Chapter 7** factors associated with both full and clinical remission of asthma were identified in a cohort of asthma patients aged 5 to 14 years at initial examination. Full remission of asthma at follow-up was defined as: no asthma symptoms, no use of inhaled corticosteroids, normal lung function ($FEV_1 > 90\%$ predicted), and no BHR ($PC_{10} > 16$ mg/ml). Clinical remission was defined as no asthma symptoms and no use of inhaled corticosteroids. After a follow-up period of 30 years (age 32 to 42 years) 22% was in full remission of asthma and 52% was in clinical remission. Fifty-seven percent of subjects in clinical remission had BHR and/or a low lung function. Both full and clinical remission were associated with a higher lung function level in childhood and more improvement in FEV_1 from age 5-14 to 21-33.

Discussion

Epidemiological and Statistical aspects

All studies reported in this thesis are prospective cohort studies. In this classic epidemiological study design a group of subjects (a cohort) is selected from the population and baseline measurements are being made. Subsequently this cohort is followed-up over a certain period of time and one or more re-examinations are performed. Advantages of this study design are the strict control over the sample-selection and the prospective nature of the data collection that makes it possible to describe a time sequence between potential risk factors and health effects. Moreover, since childhood factors are measured prospectively the phenomenon of recall bias is not present. Disadvantages are the high costs involved and the risk of a relatively high loss-to-follow-up-rate. Another disadvantage is the possibility that during the course of the study the prevailing ideas about disease development and progression may change, leading to a focus on other childhood prospective risk factors that were not measured.

In all studies, except for the study on lung function decline in chapter 5, only one (chapter 2, 3, 4, and 6) or two (chapter 7) follow-up measurements were performed after the initial measurements that established the subject's membership of the cohort. Given this restricted number of measurements per subjects basic multivariable regression techniques were used to identify predictive factors from the initial measurement for the outcome parameter measured during follow-up. The predictors of interest were entered in a linear or logistic regression model while adjustment for possible confounders was performed as well. Interactions between the predictive factors were investigated and the associations were checked for non-linearity. In chapter 3 a special type of logistic regression was used, i.e. multinomial logistic regression. In this type of regression analysis the outcome parameter consists of more than two categories and risk estimates are calculated for each outcome category compared to the reference category. An alternative to this would be to stratify the analysis, e.g. perform a regression analysis on BHR-development