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 ago\(^1\)\(^-\)\(^3\). 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 children\(^4\)\(^-\)\(^6\) or living on a farm during the first years of life\(^7\)\(^-\)\(^10\) 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 siblings\(^5\). 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 adulthood\(^11\)\(^-\)\(^18\). 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 1985 in Groningen, The Netherlands, offered us the possibility of studying asthma at a young adult age, without pre-existing factors that predispose to asthma.

In Chapter 2 risk factors for developing asthma at a young adult age were studied. A total of 38 respondents reported at least one symptom of asthma within the last year, more than males. Taking into account all possible risk factors associated with a respiratory illness (cough, cold, or dyspnoea) and with a respiratory illness (cough, cold, or dyspnoea) and with asthma, it was found that exposure during the first year of life to other children was associated with a lower risk for asthma. Smoking during the first years of life was also associated with a lower risk for asthma. Having a brother with asthma was associated with a lower risk for asthma, while a parental history of asthma was associated with a higher risk for asthma. Having a brother with asthma was associated with a lower risk for asthma.

Predictive factors for a poor outcome in asthma in Chapter 3. Apart from the risk factors previously mentioned, the child were also included in the analysis, i.e. forceps, or a caesarean section as mode of delivery, reading or medication, and possible maternal smoking during pregnancy. The child had BHR and almost all children with asthma had a severe symptom duration longer than 12 months. Of the children with asthma, having had a severe symptom duration longer than 12 months. Of the children with asthma and a severe symptom duration longer than 12 months, 31% had BHR. The child was exposed to smoke during the first years of life, and there was no decreased risk for the development of asthma. There was no association between having been breastfed for more than 6 months and the development of asthma. The child was exposed to smoke during the first years of life, and there was no decreased risk for the development of asthma. There was no association between having been breastfed for more than 6 months and the development of asthma.

Chapters 4 to 7 contain the results of the study of worsening of asthma in the first 5 years after diagnosis. The development of asthma and the progression of asthma factors that are pre-
Summary, discussion, and future perspectives

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 Netherlands, 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 (Kco), 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 Kco. It was concluded that although a reduced Kco 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 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 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

In Chapter 7 factor analysis identified in a cohort of adolescents and young adults the combination of inhaled corticosteroids, treatment for BHR (PC₂₀ > 16 mg⁄ml), and no use of inhalers after 42 years was associated with 22% was no longer asthmatic. Fifty-seven percent had a normal Kco and no symptoms, 42% had normal FEV₁ and uncorrected BHR (PC₂₀ > 16 mg⁄ml) and no use of inhalers after 42 years, and 22% was asthmatic.

Discussion

Epidemiological analysis

All studies reported that smoking is an important risk factor for the development of asthma. In epidemiological studies, a relation between smoking and the risk of asthma have been observed in the initial population and based on this, a follow-up over a certain period of time has been performed. Advantages of this approach are the possibility to describe a time sequence of risk factors and the ability to perform micro-level analysis. Moreover, since children and adolescents have a relatively high loss to follow-up during the course of follow-up studies, progression may change during the course of follow-up. This may change the predictive factors that were not detected in the initial population.

In all studies, except for those that included asthma in childhood a negative association between smoking and asthma have been found. In chapter 2, 3, 4, and 5, the predictive factors were defined after the initial measurement of asthma. Given this restriction, a multivariable regression model was performed to determine the initial measurement of asthma and the predictors of interest. Adjustment for possible confounders and the predictive factors was performed to determine the relative contribution of each factor to the risk of asthma. This model consists of more than one predictor, and the relative contribution of each predictor is calculated using logistic regression. The outcome category of interest was remission of asthma.
fully reversible group of patients a result of 26 years, less BHR at initial airway symptoms and a reduced incidence of 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 FEV₁ 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.