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Chapter 1

General introduction and aims of the thesis

ADULT-ONSET ASTHMA, SUBPHENOTYPING AND IDENTIFIYING SEVERE DISEASE

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role[1]. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, coughing and sputum production[1]. Asthma affects people of all ages, all over the world with different grades of severity, ranging from very mild intermittent disease to very severe disabling disease. This latter group is estimated to account for approximately 5-10% of all patients with asthma and in these patients significant (co)morbidity is often associated with the disease[2].

The development and expression of asthma are influenced by many factors, such as genetics, gender and body weight, as well as environmental factors, such as allergens, infections, occupational sensitizers, smoking and air pollution, and thereby complicates effective clinical care[1]. In addition, because of this heterogeneity there is no clear definition of asthma and defining this complex disease is often by (clinical) characteristics that can be objectively measured, so called phenotypes[3]. A phenotype is defined as the "observable properties of an organism that are produced by the interaction of the genotype and the environment" and, in asthma, are often defined by clinical or physiological factors (i.e. atopy or severity), triggers of onset (i.e. occupational, exercise) or pathobiology (i.e. eosinophilic or neutrophilic asthma)[3].

The classical, most prevalent phenotype of asthma is associated with atopy, starts in early childhood, and typically runs in families[4]. This type of asthma has been extensively studied in in-vivo and in-vitro asthma models, and can be reasonably well controlled by current anti-asthma medications. However, there is an increasing awareness that there is another phenotype that differentiates from early-onset asthma, the adult-onset asthma. Currently, it has been shown that adult-onset asthma in general affects more women than men[5-7], is more often non atopic[8-10], is more severe at onset[11], more likely to persist[11] and shows a faster decline in lung function as compared to patients with asthma that started in childhood[12]. Also, adult-onset asthma is a more heterogeneous disease because it is affected by a mix of allergic, infectious and other factors, resulting in many complex manifestations of adult-onset disease with different responses to treatment[3].

However, to better understand severe adult-onset asthma, disease mechanisms and to identify relevant clinically well recognized subphenotypes of adult-onset asthma for more personalized targeted therapies, further research in this phenotype is needed. Therefore, this thesis will focus on the severe adult-onset asthma phenotype and factors associated with, more severe, disease outcome.

To that end, a cohort of 200 patients with adult-onset asthma were characterized by clinical, functional and inflammatory markers and cross-sectionally evaluated.

EVALUATING SEVERE ASTHMA.

Phenotyping and defining patients with severe asthma is increasingly important for the development of new targeted therapies, as patients with uncontrolled disease with maximal dose of therapy, eventually might become well controlled with a phenotype specific approach. However, before patients are eligible for such therapies, aggravating factors that influence asthma control should be thoroughly checked. Recently, the Innovative Medicine Initiative (IMI) stated in an international consensus statement that patients with difficult-to-control asthma should be checked according to an algorithm before being diagnosed with severe, refractory asthma[13]. This algorithm includes compliance, inhalation technique and treatment of co-morbidities. The co-morbidities anxiety and depression have been associated with asthma, although the association with asthma severity is controversial[14-17]. Despite this, it has been clearly demonstrated that psychiatric morbidity in asthma is associated with reduced adherence to treatment[18], loss of asthma control[19], increased medical consumption[16] and increased exacerbations requiring bursts of oral corticosteroids[20].

Another factor that is included in the IMI algorithm is adherence. Poor adherence has been associated with poor outcomes, hospital admissions, emergency department visits and use of oral corticosteroids[21;22]. Adherence rates in patients with asthma have been estimated between 30-70%[21;23-25]. However, these numbers need to be validated in larger cohorts of patients with difficult-to-control asthma in primary and secondary care.

Therefore the last part of this thesis will focus on adherence in patients with difficult-to-treat asthma and the prevalence of the co-morbidities anxiety and depression in mild, severe and prednisone-dependent asthma. As these topics are important for all phenotypes of asthma, these research questions were investigated in large cohorts of asthma patients of all kinds of phenotypes.

OBJECTIVES OF THE THESIS

1. To characterize adult-onset asthma and identify subphenotypes of adult-onset asthma.
2. To investigate whether disease severity in patients with adult-onset asthma is associated with specific phenotypic (clinical, functional and inflammatory) characteristics.
3. To assess the frequency of CRS (including nasal polyposis) in adult-onset asthma, and to investigate if the severity of chronic rhinosinusitis and presence of nasal polyps is related to the severity of lower airway inflammation.
4. To investigate whether several potential risk factors (age, age of asthma onset, asthma duration, gender, BMI, smoking history, race, absence of atopy and use of oral corticosteroids) are associated with persistent airflow limitation in patients with adult-onset asthma.

5. To investigate the prevalence of anxiety and depression symptoms in patients with severe, prednisone-dependent asthma and to investigate whether these patients have elevated dysfunctional personality traits as compared to patients with severe, non-prednisone-dependent and mild-moderate disease
6. To investigate the adherence of inhaled corticosteroids in patients with asthma, but also with other respiratory diseases.

OUTLINE OF THE THESIS

In chapter 3 we describe three different subphenotypes that can be identified in adult-onset asthma, with distinct clinical and inflammatory features. In chapter 4 we investigated whether disease severity in patients with adult-onset asthma is associated with specific phenotypic (clinical, functional and inflammatory) characteristics

In chapter 5 we investigate the prevalence of chronic rhinosinusitis and nasal polyposis in newly diagnosed adult-onset asthma and assess if the severity of chronic rhinosinusitis in these patients is correlated with the intensity of eosinophilic inflammation in the lower airways and in chapter 6 we assessed risk factors associated with persistent airflow obstruction in adult-onset disease.

When diagnosing severe asthma it is important to exclude comorbidity or non-adherence as the reason for lack of control. Therefore in chapter 7, we assessed the prevalence of several of these co-morbidities (e.g. anxiety and depression) in asthma, irrespective of age of onset. Finally, in chapter 8 we assessed the prevalence of non-adherence to inhaled corticosteroid treatment in patients with severe uncontrolled airway disease. In addition, we assessed factors associated with adherence to inhaled corticosteroid treatment in general, and more specifically in asthma.

Chapter 9 summarizes the most important findings of this theses and clinical and research implications are discussed.

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Chapter 2

Adult-onset asthma: a neglected asthma phenotype

M. Amelink, E.H. Bel

ADULT-ONSET ASTHMA

Asthma is known as a disease typically associated with children, but since the middle of the 20th century it has been appreciated that it can have its onset in adulthood as well[1]. In fact, asthma can appear at any age[2], even in the elderly[3]. Surprisingly, adult-onset asthma had never been investigated systematically, until the last decade, when Miranda and colleagues first described the phenotypic differences between patients with early-onset and adult-onset asthma[4]. This resulted in an increasing awareness that this specific phenotype differentiates from early-onset (childhood) asthma [5].

EPIDEMIOLOGY

There are relatively few studies that have investigated the incidence of adult-onset asthma. In a systematic review of general population studies on the incidence of asthma, the pooled estimate of the adult incidence of asthma was 4.6/1000 per year for women and 3.6/1000 per year for men with a trend towards higher estimates of adult incidence in later studies[4]. The remission rate of adult-onset asthma appears to be very low, with several studies showing a remission rate between the 3% and 20% [3;6;7]. The prevalence of adult-onset asthma is even less known, and depends on the population under investigation. Amongst patients with severe asthma, the prevalence may be as high as 50%[8], whereas the prevalence in the general asthma population is much lower suggesting that adult-onset asthma is more severe, and less easy to control.

RISK FACTORS

Whilst asthma in childhood is mostly associated with early exposure to specific allergens and early infection with rhinovirus, in adults other etiologic factors have been implicated. In about 10% of the adult-onset asthma population, occupational agents are involved[9;10]. If occupational asthma is suspected, a systematic inquiry about work history and possible exposure is neededs[11]. Other risk factors for adult-onset asthma include changes in female sex hormones[12;13], cigarette smoking, regular use of acetaminophen[14], stressful life events[15], obesity, and specific respiratory infections, such as Mycoplasma pneumoniae or Chlamydia pneumoniae[16].

CLINICAL PHENOTYPES

Despite increasing awareness, adult-onset asthma is still poorly understood, mostly because the vast majority of all asthma research focuses on childhood onset allergic asthma. With respect to clinical characteristics, adult-onset asthma in general affects more women than men[2;17], is more often non atopic [1], is more severe at onset[18], more likely to persist[6;18] and shows a faster decline in lung function as compared to patients with asthma that started in childhood[8;19;20]. In addition, this phenotype of asthma is more often associated with nasal polyposis[21] and aspirin intolerance[22], the latter especially when the age of onset increases[21]. Also, adult-onset asthma is a more heterogeneous disease as compared to childhood onset asthma which is more homogeneous[5], probably because adult-onset asthma is affected by a mix of allergic, infectious and other factors[5].

More recently, three studies using cluster analysis have identified distinct, clinically well recognized, phenotypes of patients with adult-onset asthma[23-25].

This first subphenotype is the non-atopic, inflammation predominant phenotype with fixed airflow limitation. This phenotype consists of mainly males with few daily symptoms and is typically characterized by the presence of sputum eosinophilia, which could be considered the key characteristic of this phenotype[26]. It has been shown that this phenotype is consistent over time and independently associated with extensive sinus disease[26]. Clinically, the persistence of eosinophilia has important implications as it has been associated with asthma exacerbations[27], persistent airflow limitation[28], and oral corticosteroid dependence[29]. Also, in patients with extensive sinus disease it has been shown that they have more often sputum eosinophils in the lower airways[30] and more often air trapping on CT-scanning, indicating more small airway involvement in this group of patients[30;31].

The second subphenotype, the late onset obese female preponderant phenotype, consists of mainly female patients with relatively high BMI, less atopy, and a high symptom expression[23-25]. There exists a strong association between body mass index and the risk of adult-onset asthma[32;33], and the prevalence of obesity in the developing countries is increasing. Therefore, it is to be expected that the prevalence of this phenotype will increase as well. The mechanistic basis of the relationship between obesity and asthma has not been completely identified, although several mechanical and inflammatory contributing factors have been suggested[34-36]. Clinically, obesity has been associated with a reduction of therapeutic effect of inhaled corticosteroids with regard to airway inflammation and lung function[37] and a blunted response to dexamethasone[38] and in contrast to the inflammation predominant phenotype, a higher body mass index in asthma has been found to be inversely related to sputum eosinophils and exhaled FeNO[34]. Co-morbidities including gastroesophageal reflux (GERD)[36] and sleep-disordered breathing[36] are highly prevalent and may contribute to poor asthma control. Not surprisingly, obesity in asthma has been associated with more severe

symptoms [39], poorer asthma control[39;40], lower lung functions[41], and more frequent medical visits and hospitalisations[39].

Besides these subphenotypes of adult-onset asthma identified by cluster analyses, several other subtypes of adult-onset asthma have been described in the literature.

Firstly, occupational asthma, a subtype of adult-onset asthma in which a clear occupational inciting agent can be distinguished, [42;43]. This important asthma subtype has been implicated in 9-15% of the cases of adult-onset asthma and has been well investigated[9;10]. Clinical, functional and pathological changes in occupational asthma are similar to other types of asthma[44], although after cessation of the occupational agent 50% remains symptomatic and/or maintain lung function abnormalities[45].

Secondly, the often unrecognized, type of asthma that develops in smokers, or shortly after smoking cessation[46]. Smoking has been identified as a risk factor for developing adult-onset asthma[46] and one study investigating the prevalence of adult-onset asthma showed that more than half of the patients had a history of prior tobacco use[3]. In addition, in older patients the manifestations of asthma and COPD can be similar and consequently it can be difficult to distinguish between the two conditions, despite different causes and mechanisms[47].

Finally, non-eosinophilic or neutrophilic asthma, which is characterized by increased numbers of neutrophils in the airways. This type of asthma affects mostly patients with severe asthma[48], is associated with a poor response to corticosteroids[49], and is frequently triggered by viral infections[50]. Because COPD is also known as a disease with typically neutrophilic inflammation, it has been suggested that neutrophilic asthma is a form of COPD. However, studies have shown that the radiographic change of the bronchial wall in neutrophilic asthma is different from that in smokers and patients with COPD, and that it is a distinct asthma subtype[51].

For the management and treatment of adult-onset asthma it is important to categorize patients into these different subtypes, because treatment regimens, comorbidities and risk factors for asthma severity differ between these subtypes.

APPROACH OF THE PATIENT WITH ADULT-ONSET ASTHMA

Adult-onset asthma is often underdiagnosed and misdiagnosed. Many adult patients with respiratory symptoms are not aware that they have asthma, as they often ascribe their symptoms to other diseases or aging itself[52;53]. Asthma symptoms can be intermittent and their significance may be overlooked because they are non-specific [54-56] Thus, it may take years for symptoms to be recognized as asthma symptoms, which leads to delays in diagnosis and treatment[52]. Physicians are often not aware of the prevalence of adult-onset asthma. In addition, there can be overlap between the symptoms of asthma and other older-age related

diseases, including heart failure, bronchiectasis and chronic bronchitis[55-57]. In particular in patients with a history of smoking a misdiagnosis of COPD is easily made. Wheeze can be a sign of pulmonary congestion, whilst cough can be induced by medication, gastroesophageal reflux, postnasal drip, chronic sinusitis and vocal cord dysfunction[55]. Also chest tightness can be a symptom of gastroesophageal reflux, cardiac disease or anxiety.
Therefore, it is important to be fast en correct in making the diagnosis in order to prevent disease progression and lung function decline.

ASSESSMENT OF COMORBIDITIES

After a diagnosis of adult-onset has been made, phenotypic comorbidities need to be addressed. In patients with the "non-atopic", inflammation predominant asthma subtype special attention should be paid to the detection of hidden allergies, in particularly (mono-) sensitization to moulds, as this has been associated with an increased risk for adult-onset asthma[58] and reduced lung function[59]. Furthermore, presence of (persistent) eosinophilia in blood and sputum, assessment of small airway disease, and whenever possible an aspirin provocation tests should be performed. In addition, patients sinonasal assessment by means of CT-scanning or nasal endoscopy is needed, because patients with sinonasal disease often do not report nasal symptoms [60;61].
In patients with the obese female preponderant asthma subtype blood en sputum should be checked for eosinophils and/or neutrophils. Absence of eosinophils is typical, and neutrophilia is common. Also, waist circumference should be assessed as an increased waist circumference has been associated with more severe asthma[62]. Moreover, physicians should be particularly aware of the co-morbidities that are prevalent in this type of asthma and may provoke asthma symptoms, such as gastroesophageal reflux (GERD)[36] and sleep-disordered breathing (SDB)[36].
It is important to characterize these different subtypes of adult-onset asthma as carefully as possible, to treat comorbidities accurately and identify possible risk factors for asthma severity so that they can be closely monitored.

THERAPEUTIC APPROACHES

The standard treatment of asthma has been well described[63] in several international guidelines such as the GINA[11], NHLBI/NEAPP[64] and BTS guidelines[65]. The therapeutic approach of patient with adult-onset asthma is similar as in childhood onset asthma. However, it could be extended towards more personalized medicine as adult-onset asthma has specific, clinically

well recognized subphenotypes with different symptoms, asthma course and co-morbidities. Therefore, every subtype needs to be individually assessed with respect to clinical, functional and inflammatory markers.

GENERAL MEASURES

Several studies have shown that asthma incidence is increased in overweight and obese men and women and that there is a relationship between body weight and asthma incidence[32;66]. Therefore, it could be suggested that weight reduction is essential to prevent asthma development and obtain better asthma control in the obese asthma phenotype.
Patients with occupational asthma should avoid further exposure to the causative sensitizing agent, as it has been shown that ongoing exposure can cause further impairment of the respiratory function and bronchial hyperresponsiveness[67]. And even after cessation of the occupational agent, full recovery is rather exceptional. Several studies have shown that only 50% of the patients have a decrease in asthma symptoms[67] after cessation of exposure[67].

ADDITIONAL INHALED THERAPY

Ultrafine ICS can be extra helpful in gaining asthma control as it has been shown that they decrease het number of eosinophils in de lungs[68] and reduce the number of asthma exacerbations[69]. Especially patients with small airway disease, which has been associated with the eosinophilic predominant phenotype with extensive sinus disease with nasal polyposis[26 30;31], could benefit from ultrafine ICS. Also, leukotriene modifiers have a small bronchodilator effect, reduce symptoms[70], improve lung function, and reduce airway inflammation and exacerbations[71-73]. As add-on therapy it can reduce the dose of ICS[74], or may lead to better control[75;76], especially in patients with aspirin sensitivity[77;78].
There is a subgroup of patients with severe asthma remains uncontrolled despite high dose ICS. These patients often need chronic oral corticosteroids to control their symptoms. Unfortunately, this is often the case in patients with the non-atopic, inflammation predominant type of asthma, with nasal polyposis and/or aspirin sensitivity[22]. In patients with OCS dependent asthma, special attention is also needed for the many systemic side effects.
Last, Omalizumab is indicated for patients with severe allergic asthma who remain uncontrolled despite adequate treatment. Addition of omalizumab reduces exacerbations and decreases corticosteroid use[79]. Although indicated for allergic asthma, a recent case reports showed that it also can be effective in non-atopic asthma[80] and in chronic rhinosinusitis with nasal

polyposis[81]. However, before the indication of omalizumab can be broadened, further clinical trials need to be conducted.

ADDITIONAL TREATMENT OPTIONS

Anti IL-5 humanised monoclonal antibody is a novel drug for patients with persistent eosinophilic asthma. It has been shown to be effective in reducing eosinophils[82;83], prevent eosinophil recruitment[84], reduce exacerbations[83;85], hospital admissions and improve asthma symptoms and control[86]. Large multicentre clinical trials are now ongoing and will hopefully lead to FDA approval. Macrolides have immunomodulatory properties that may have beneficial therapeutic effects in asthma. In asthma they are known to reduce hospital admissions, asthma symptoms, steroid use, airway hyperresponsiveness, sputum eosinophils[87] and neutrophilic counts[88]. Also, macrolides reduce sinus mucosal inflammation, eosinophils activity and even the extend of nasal polyposis in patients with chronic rhinosinusitis[89]. Therefore, macrolides can have beneficial effects in patients with asthma, especially those with the inflammation predominant type with nasal polyposis[87] or those with neutrophilic asthma[88]. However, more placebo controlled studies are needed to confirm the efficacy and safety of long-term macrolide use.

Last, high altitude treatment has been applied for many years in the treatment of pulmonary diseases in childhood and adult-onset asthma. Because of the reduced levels of house dust mite and moulds and the clean air this treatment has many positive effects on allergic asthma[90]. Additional, a recent report shows that a similar reduction in the use of systemic corticosteroids in patients with intrinsic asthma as compared to allergic asthma[93]. Therefore, this treatment could be applied for all patients with severe adult-onset asthma.

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Chapter 3

Three phenotypes of adult-onset asthma

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INTRODUCTION

Asthma is a heterogeneous disease driven by a mix of genetic and environmental factors[1;2]. Because of this heterogeneity the term asthma is not clearly defined. Consequently, the clinical diagnosis of asthma and asthma severity are based on characteristics such as lung function and symptom[1]. However, there is increasing evidence that this approach does not reflect the multidimensional nature of the disease[2;3]. Therefore, identification of different asthma phenotypes is of increasing importance[4].

Recently, several studies have used cluster analysis in different groups of asthma patients to identify clinically well recognized phenotypes of asthma[5-7]. By using these multivariate techniques several adult phenotypes could be identified with clinically important differences. On the one hand they found phenotypes of asthma that started in childhood including early onset atopic asthma[5-7] benign asthma[5-7] and symptom predominant asthma[6]. On the other hand, the cluster analysis also revealed two clusters of asthma starting mainly in adulthood, the noneosinophilic obese female cluster[5-7], and a cluster with predominantly males with eosinophilic asthma[6].

Not much is known about the mechanisms of adult-onset asthma phenotype. In 2002 Miranda and colleagues described phenotypic differences between patients with early-onset and adult-onset asthma[8], resulting in an increasing awareness that this phenotype differentiates from early-onset (childhood) asthma[9-13]. Ever since, it has been shown that it is more heterogeneous, often severe[10], and frequently associated with loss of lung function[11-13]. In addition, whilst childhood-onset asthma is mostly atopic in nature[14], adult-onset asthma is often associated with specific triggers such as respiratory tract infections[15], exposure to occupational agents[16], aspirin intake[17], smoking[18] and obesity suggesting different underlying mechanisms.

However, to identify these mechanisms detailed characterisation and subphenotyping of adult-onset asthma is necessary. In the present study, we hypothesized that adult-onset asthma is heterogeneous and can be divided into various subphenotypes. Therefore we used unbiased non-hierarchical cluster analysis techniques to identify these subphenotypes.

METHODS

Subjects

A total of 200 subjects with adult-onset asthma were recruited from 1 academic and 3 non-academic hospitals in Amsterdam, The Netherlands, between June 2009 and June 2011. Eligible subjects were adults (20-75) with a physicians diagnosis of asthma that started

after the age of 18, who were stable on asthma medication (no exacerbations or changes in asthma medication in the past 4 weeks). Asthma was defined according to GINA criteria[1]. Exclusion criteria were: any respiratory symptoms or chronic lung diseases during childhood, other pulmonary diseases including COPD, or non-related major co-morbidities.
Current and ex-smoking (>10py) was allowed if the patient had at least 12% improvement in FEV_1 after inhalation of 400ug salbutamol and a normal diffusion capacity at the time of inclusion[20]. This study was approved by the hospital Medical Ethics Board (MEC 08/358; NTR number 1838) and all patients provided written informed consent.

Study Design

During this cross-sectional multicenter study all patients fulfilled questionnaires that assessed demographic data, medical history, medical consumption and medication use, as well as the Asthma Control Questionnaire (ACQ)[21], the Asthma Quality of Life Questionnaire (AQLQ)[22] and the Sino-Nasal Outcome Test-22 (SNOT-22)[23]. Physiologic testing of lung function included pre- and postbronchodilator spirometry, carbon monoxide diffusion capacity, body plethysmography and, if possible, bronchial hyperresponsiveness to methacholine[24-26]. Atopic status was assessed by total IgE and specific IgE to a panel of common aero- and food allergens by using the Pharmacia Uni-CAP System. In addition, all patients were assessed for specific IgE to Aspergillus fumigatus. Inflammatory status was measured by the fraction of exhaled nitric oxide (FeNO), assessment of neutrophils and eosinophils in peripheral blood and induced sputum[27.]

Statistical Analyses

Data reduction and variable selection:

The total number of variables was reduced by elimination of data irrelevant for the current analyses or that were in written text format. With respect to lung function measurements the clinical most relevant parameters were chosen. Demographic data were selected to cover a broad variety of routine assessments, as were data on disease severity. Eventually, a total of 35 variables were selected based on clinical relevance and avoiding redundance. After initial data selection missing data were imputed and further reduced by factor analyses with orthogonal varimax rotation. Based on the pattern of loading 11 factors were identified with Eigen value >1.

Cluster Analysis:

Cluster analysis was performed in a multi-step approach. First, Ward's hierarchical cluster analysis was used for estimation of the number of likely clusters. Then cluster quality was checked by two-step cluster analysis methods and K-means non-hierarchical cluster analysis was performed. To ensure repeatability and stability within the model, the K-means algorithm was repeated 199 times in a leave-one-out validation model.

Other statistical methodology:

Non-normally distributed data were log transformed before initial analysis. For comparison between clusters X^2- tests were used for proportions and ANOVA with post-hoc analysis for parametric variables. All analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL). P-values less than 0.05 were considered statistically significant.

RESULTS

Subject demographics

In total 832 patients visiting the outpatient clinic were screened for the present study, of which 306 patients had a (possible) diagnosis of adult-onset asthma. However, 106 recollected childhood dyspnea or asthma, did not meet the inclusion criteria or refused to attend for various reasons. Therefore 200 patients with adult-onset asthma were enrolled in the present study, consisting of secondary and tertiary care patients, either referred by the general practitioner (70%) or by a pulmonologist (30%). Patients were aged between 26-75 and the majority of them being female (60.5%). The results show that patients with adult-onset asthma are mainly non-atopic (55%) and only 39% reported a positive family history for asthma. With respect to medication use and health care utilisation, 41.5% used a high dose of inhaled corticosteroids (ICS), 23% used daily oral corticosteroids (OCS), and 26% had at least 3 or more exacerbations that required OCS in the past 12 months. Of all patients with adult-onset asthma 38.5% met the IMI-criteria of severe asthma(28). In addition, a large proportion (51%) of these patients showed elevated sputum eosinophils (median (range) 2.1 (0.2-16.4)), despite adequate treatment with inhaled corticosteroids. Baseline demographics and clinical data of the complete cohort are given in Table 1. Data on medical history, medication use and health care utilisation are given in Table 2.

Table 1. Baseline characteristics of the total cohort and individual clusters.

	Total Cohort (n=200)	Cluster 1 (n= 69)	Cluster 2 (n=41)	Cluster 3 (n= 90)	p-value
Female %	60.5	71	68.3	48.9	0.01
Age*	53.9 (10.8)	54.8 (9.7)	53 (9.7)	53.7 (12)	0.7
Age of onset*	41 (12.8)	40.6 (12.4)	41.5 (12.2)	41.1 (13.5)	0.9
Asthma duration†	10 (4-20)	10 (6.5-20)	8 (4-19.5)	8.5 (3-21)	0.09
Body Mass Index*	28 (4.9)	28.2 (5)	30.4 (5.4)	26.7 (4.3)	<0.001
Caucasian Race %	85	85.5	65.9	93.3	<0.001
Packyears†	0 (0-7.4)	1 (0-13.5)	0 (0-2.5)	0 (0-7.2)	0.15
Total IgE†	105 (33-599)	119 (47-407)	84 (51-372)	97 (26-263)	0.29
Atopy – inh. allergens%	45	43.5	48.8	44.4	0.85
Atopy – food allergens%	8	5.8	7.3	10	0.61
Atopy – Asp. Fumigatus%	10.5	5.8	12.2	13.3	0.28
History of Nasal Polyposis%	37	42	31.7	35.6	0.51
Lung function:					
pbFVC %pred*	106.6 (19.9)	105 (18.4)	94.4 (19.1)	113 (18.4)	<0.001
pbFEV1 %pred*	91.8 (20.9)	84.4 (21)	83.9 (21.1)	101.1 (16.7)	<0.001
pbFEV1/FVC %pred*	91 (14.8)	85.6 (15.6)	94.3 (14.1)	93.6 (13.4)	<0.001
Change in FEV1 %pred†	5 (2-10)	7 (2-11)	4 (2-7.5)	5 (2-10)	0.29
KCO %pred*	101.2 (16.4)	100.7 (18.5)	103.4 (15.3)	100.5 (15.2)	0.62
pbRV/TLC %pred*	92.8 (19.4)	100.9 (19.8)	97.6 (20.6)	84.4 (15)	<0.001
PC20	2.5 (19.5)	0.6 (19.5)	2.5 (19.5)	3.9 (19.5)	0.002
FeNO.ppb†	28.7 (16.2-59.3)	34 (17-70)	20.7 (11.4-39)	28 (17-59)	0.03
Sputum eosinophils (%)†	2.1 (0.2-16.4)	6.3 (0.3-24.7)	0.9 (0.1-18)	1.4 (0.1-9.9)	0.048
Sputum neutrophils (%)†	69.7 (45-84.6)	63.1 (39.5-83.6)	74 (61-93.7)	68.7 (43.7-84.6)	0.46
Blood eosinophils.109/l †	0.2 (0.1-0.34)	0.3 (0.11-0.51)	0.18 (0.1-0.28)	0.19 (0.01-0.3)	0.17
Blood neutrophils.109/l †	4.3 (3.4-5.8)	4.4 (3.8-6.1)	4.3 (3.2-6.5)	4.2 (3.2-5.4)	0.29

p-value from Anova or X^2 analysis between the three clusters.
FVC = Forced Vital Capacity; FEV1 = Forced expiratory flow in 1 second; KCO = Transfer coefficient expressing carbon monoxide diffusing capacity; RV = Residual volume; TLC = Total lung capacity; pb = post bronchodilator; FeNO = fraction of exhaled nitric oxide
Data is represented in *mean(±SD); †Median (interquartile range) or frequency (%).

Subphenotyping adult-onset asthma

Using Wards and K-means cluster analysis we identified 3 subphenotypes of patients with adult-onset asthma separated by gender, BMI, lung function, sputum eosinophils, sensitivity to NSAIDs or aspirin and asthma quality of life. Baseline demographics and clinical data are given in Table 1. Data on medication and health care use is given in Table 2.

Table 2. Medical History, medication use and health care utilization

	Total Cohort (n=200)	Cluster 1 (n = 69)	Cluster 2 (n = 41)	Cluster 3 (n = 90)	p-value
Reflux medication/symptoms %	52	50.7	75.6	42.2	<0.01
Hormonal induced symptoms %F	18.5	20.3	19.5	16.7	<0.01
NSAID sensitivity %	15	5.8	17.1	21.1	0.02
Familial Asthma %	39	40	46	35	0.48
Familial Atopy %	33	36.2	29.3	32.2	0.78
Occupational asthma %	5	5.8	2.4	5.6	0.69
home environmental triggers %	0.5	1.4	4.9	4.4	0.72
Nasal corticosteroids %	57	47.8	70.7	57.8	0.06
Cronic Oral Corticosteroids %	23	26.2	31.7	16.7	0.13
Dose of Oral Corticosteroids†	7.5 (5-10)	10 (5-10)	7.5 (5-15)	7.5 (5-10)	0.13
Dose of ICS†	500 (500-1000)	1000 (500-1000)	1000 (500-1000)	500 (0-1000)	0.02
Omalizumab %	6	7.2	12.2	2.2	0.07
Exacerbations <12mths %					<0.001
- 0	52.5	42	29.3	71.1	
- 1-2	21.5	29	17.1	17.8	
- > 3	26	29	53.7	11.1	
Hospital of inclusion %					0.004
- Secondary care	27.5	15.9	22	38.9	
- Tertiary care	72.5	84.1	78	61.1	
Doctors visits <12mths %					<0.001
- 0	8	2.9	4.9	13.3	
- 1-2	48	40.6	24.4	64.4	
- > 3	44	56.5	70.7	22.2	
ACQ-score*	1.5 (1)	1.9 (0.8)	2.5 (0.8)	0.7 (0.6)	<0.001
AQLQ-score*	5.2 (2.2)	5 (0.4)	3.2 (0.8)	6.2 (0.4)	<0.001
SNOT-score*	1.2 (0.9)	1.4 (0.6)	1.9 (0.9)	0.9 (0.6)	<0.001

p-value from Anova or X^2 analysis between the three clusters.
ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; SNOT-22 Sino-Nasal Outcome Test-22; ICS = inhaled corticosteroids fluticason equivalent
Data is represented in *mean(±SD); †Median (interquartile range) or frequency (%).

Cluster 1: severe eosinophilic inflammation-predominant

The first group we identified consisted of 69 (34.5%) patients, and described a severe eosinophilic inflammation-predominant group with persistent airflow limitation. This group was characterized by predominantly females (71%) with a postbronchodilator FEV_1/FVC percentage predicted of 85.6% (+15.5), increased exhaled FeNO levels and increased sputum eosinophil percentages (6.3% (0.3-24.7)) These patients were treated with medium to high doses of ICS, in 26% of the cases combined with maintenance OCS. Twenty-nine percent

had at least three exacerbations and 13% had at least one hospitalisation or emergency department visit in the past 12 months.

Cluster 2: frequent symptoms, high health care utilisation and low sputum eosinophils

The second subphenotype (n = 41, 20.5%) had a higher prevalence of patients of non-Caucasian descent and was characterized by obese females with frequent symptoms, high health care utilisation and low sputum eosinophils. Patients in this cluster had the highest symptom scores and were the most often treated for gastroesophageal reflux disease (GERD) or had complaints of GERD. Their postbronchodilator FEV_1 was reduced, but their FEV_1/VC ratio was normal. They were treated with high dose ICS often combined with OCS or anti-IgE treatment. Despite these high treatment regimens they had the most frequent doctors' visits (70.7%), exacerbations (53.7%), and hospitalisations or emergency department visits (31.8%). These symptoms and high health care utilisation seemed to be out of proportion with their clinical and inflammatory markers as they showed no airways obstruction, low FeNO levels and low sputum eosinophils counts.

Cluster 3: mild to moderate, well controlled asthma

The third cluster was the largest and consisted of 90 patients (45%) with a mild to moderate, well controlled asthma. This group has a male preponderance of Caucasian descent and more often a history of aspirin sensitivity. Symptom scores, lung function measurements and airway inflammation were often within the normal range and these patients were mostly treated with an intermediate dose of ICS. In addition, patients in this cluster had the lowest number of exacerbations (29%) and hospitalisations or emergency department visits (5.6%) in the past 12 months.

Validation

To ensure repeatability and stability within the model, the k-means algorithm was repeated 199 times in a leave-one-out validation model. This showed a within repeatability accuracy of 98.2%.

DISCUSSION

Three subphenotypes of adult-onset asthma were identified in the present study. The first cluster consisted of patients with severe eosinophilic inflammation-predominant asthma with persistent airflow limitation and few asthma symptoms. The second subphenotype was characterized by obese females with frequent asthma symptoms and high health care utilisation, but normal lung function and low sputum eosinophils. The third cluster showed patients with mild to moderate, well controlled asthma with normal lung function and low inflammatory markers.

These results reinforce the existence of two previously described clusters of mainly severe asthma patients (obese female and persistent eosinophilic) that together covered about half of the patients with adult-onset asthma, and a third cluster of patients with well-controlled, mild asthma, covering the other half. Other clinically significant clusters were not identified. Our results confirm that the previously described clusters of adult-onset severe asthma are distinct and robust, and require a personalized management approach.

The present study is, to our knowledge, the first to thoroughly describe a large cohort of patients with adult-onset asthma with respect to clinical, functional and inflammatory markers. It shows that adult-onset asthma affects more women than men, that the majority of patients are non-atopic and that there is a high prevalence of severe disease, which has been suggested in previous studies as well[9-13]. The clusters we identified in the present study are in agreement with previous findings in heterogeneous populations of patients with asthma[5-7].

In our study we identified a subset of mainly female patients with severe eosinophilic inflammation-predominant asthma, few asthma symptoms and persistent airflow limitation. This fits in with one of the adult-onset asthma clusters in the study by Haldar and colleagues that consisted of patients with active eosinophilic inflammation and few daily symptoms, although they found predominantly males in this cluster[6]. Our results not only confirm the existence of this important adult-onset asthma phenotype, but also more sharply delineates its phenotypic characteristics in an independent population with different treatment strategies.

Remarkably, a high percentage of patients with eosinophilic inflammation showed incomplete reversibility of FEV_1, which fits in the results of several previous studies, showing that patients with adult-onset asthma are at increased risk of fixed airflow limitation[11-13]. This suggests that in this specific subphenotype of asthma aggressive remodelling processes might be active. In addition, there is now convincing evidence that it is associated with increased risk of asthma

exacerbations[29], persistent airflow limitation[30], and oral corticosteroid dependence[31]. This implies that a symptom guided management approach may not be effective in these patients and an inflammation targeted management e.g. with monoclonal antibodies against anti IL-5[32] is warranted to prevent future exacerbations and lung function decline.

The second group of patients with adult-onset asthma that was identified consisted mainly of obese females with high healthcare utilisation. By using the similar clustering techniques as Haldar, we could reproduce and extend these important previous results in a cohort of secondary and tertiary care patients with adult-onset asthma in the Netherlands. We also confirmed that this obese adult-onset asthma phenotype is not associated with eosinophilic airway inflammation[33] and responsiveness to inhaled corticosteroids[34] but is characterized by poor asthma control, low quality of life and high health care utilization. Apparently, other mechanisms are causing asthma symptoms in these patients, including altered lung mechanics, leading to airway hyperresponsiveness and increased airway smooth muscle stiffness[35]. It has also been shown that visceral adipose tissue in obese adult-onset asthma patients produces high levels of adipokines, which is associated with airway reactivity but not with airway inflammation[36]. And finally, overweight patients may exhibit co-morbidities that provoke or worsen asthma, in particular gastroesophageal reflux (GERD)[35]. By consequence, a management strategy aimed at reducing overweight rather than reducing airways inflammation might be indicated in these patients to prevent overtreatment with corticosteroids.

Apart from these two subphenotypes of patients with severe and uncontrolled asthma, the present study identified an additional third cluster of mild to moderate persistent, well controlled adult-onset asthma. It consisted almost exclusively of Caucasians, and was mainly recruited from secondary care clinics. We were not surprised that these patients with mild-moderate adult-onset asthma constituted the largest cluster. A prospective study investigating outcome and severity of all incident cases of adult-onset asthma in the northern part of Sweden showed that after a follow-up period of 5-10 years 70% of the patients had developed mild to moderate persistent disease[10], whereas only 5% had developed severe disease. Very recently, another cluster analyses in Korean patients showed a cluster of mild adult-onset asthma[37]. Our study confirms this specific adult-asthma subphenotype, thereby showing that adult-onset asthma is not always severe or uncontrolled, but can also have a milder course and prognosis.

Although the present study was performed in a well characterized cohort of patients with adult-onset asthma and a validated unsupervised approach was used for the analysis, it might have some limitations. First, the age of onset and duration of asthma were based on

self-report and could therefore be influenced by recall bias. Despite stringent inclusion and exclusion criteria, we cannot exclude this bias entirely, although in one study the reported year of asthma onset appeared to be rather accurate[38]. Second, although every effort was made to insure as much objectivity as possible, several subjective areas needed to be addressed in the cluster analysis, such as the choice of variables used for the analysis and the optimal number of clusters. Although we used a broad selection of variables and let factor analysis decide which variables would eventually be used in the analysis, we cannot exclude the possibility that variables of greater significance were excluded by this process. However, the present study has identified clinically well recognized subphenotypes that were identified in previous studies using similar and different clustering techniques in different populations. Therefore, we do not think that the subjective areas that needed to be addressed had a great influence on our results. Third, the persistent eosinophilia in one of our clusters might be related to non-adherence rather than being a reflection of more severe asthma[39], which we cannot exclude and warrants further investigation. Fourth, the patients in our study were recruited from secondary and tertiary outpatient clinics. Since patients with mild asthma in The Netherlands are mostly treated by the general practitioner there might be an over-estimation of patients with more severe disease in our cohort. Therefore, we cannot estimate the real proportion of the 3 clusters in the total population of patients with adult-onset asthma.

In conclusion, the present study shows that amongst patients with adult-onset asthma three different subphenotypes can be identified with distinct clinical and inflammatory features. These results confirm and extend the phenotypic characteristics of two previously proposed clusters of severe adult-onset asthma by showing their consistency in a different population with different treatment regimens. It also shows a third subphenotype of patients with mild-moderate adult-onset asthma. The identification of these three subphenotypes may raise novel hypotheses on the mechanisms of adult-onset asthma and asthma severity, and may give clinicians new directions for more personalized management strategies.

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Chapter 4

Severe late onset asthma: a distinct phenotype.

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INTRODUCTION

It is now well recognized that asthma is a heterogeneous condition with many different subphenotypes[1]. Supervised and unsupervised cluster analyses in various asthma populations have defined several asthma subphenotypes, and have revealed that age of asthma onset is an important characteristic to distinguish these subphenotypes[2-4].

Asthma that starts in childhood has extensively been studied and has been shown to be a relatively homogeneous subphenotype, characterized by fully reversible airflow obstruction, Th2 type airway inflammation and responsiveness to inhaled corticosteroids[5,6]. Asthma that starts in adulthood has received less attention, but appears to differ from childhood onset asthma in many respects. Apart from a large variety in trigger factors associated with asthma onset including respiratory infections[7], moulds[8], cigarette smoke[9], occupational exposure[10] and environmental pollutants[11], there is also a large variability in type of airway inflammation[5], natural course of the disease[12] and disease severity[12]. Many patients with late onset asthma have mild, transient disease[12], whereas others exhibit a progressive course with frequent severe exacerbations and rapid loss of lung function[13,14].

To our knowledge, so far, the clinical and inflammatory characteristics that distinguish patients with severe, late onset asthma from those with milder forms have not been studied. This distinction is important since it might give new clues for the pathophysiology and early detection of the severe late asthma phenotype, which may improve disease outcome by early and targeted intervention.

The aim of the present study was to investigate whether disease severity in patients with late onset asthma is associated with specific phenotypic (clinical, functional and inflammatory) characteristics. To that end, we first selected patients with severe late onset asthma diagnosed according to stringent international criteria[15] and compared their characteristics with those of patients with non-severe late onset asthma. Secondly, we identified factors that were significantly associated with disease severity.

METHODS

Subjects

Subjects with mild to moderate persistent or severe late onset asthma were recruited from 1 academic and 3 non-academic pulmonary outpatient clinics in the Netherlands. Patients were eligible to enter the study if they had a physicians diagnosis of asthma onset after the age of 18, and were stable on asthma medication for at least 4 weeks. Asthma was defined as a history of episodic dyspnea and wheezing, with a documented reversibility in FEV_1 of at least 12% of the predicted value or hyperresponsiveness to inhaled methacholine chloride (PC20 < 8.0 mg/ml)(16), documented in the past 5 years. Severe asthma was defined according to international IMI-consensus criteria[15], whereas mild-moderate persistent asthma was defined according to GINA guidelines[16]. Thus, all patients with severe asthma were symptomatic (ACQ>1.5) or had experienced at least 2 exacerbations in the past 12 months, despite regular treatment with high dose inhaled corticosteroids (>1000 ug/dag fluticasone equivalent), and a second controller medication. All patients with mild-moderate persistent asthma were well controlled with a pre-bronchodilator FEV_1 >80% when treated with inhaled corticosteroids (ICS), or had mild persistent symptoms (ACQ>1.5) with a pre-bronchodilator FEV_1 >60% when treated with a maximal 500ug fluticasone equivalent per day. Patients were excluded if they had any other pulmonary diseases (including COPD), a childhood diagnosis of asthma, chronic bronchitis, dyspnea attacks (spontaneous or during exercise) or use of pulmonary medication during childhood. Current and ex-smoking (>10 packyears) was allowed provided that the patient had at least 12% improvement in FEV_1% predicted after inhalation of 400 mcg of salbutamol and a normal diffusion capacity at the time of inclusion. The present study was approved by the hospital Medical Ethics Board (MEC 08/358; NTR number 1838) and all patients provided written informed consent.

Study Design

In this cross-sectional multicenter study all patients were fully assessed during one visit. With the exception of a methacholine challenge test, this was performed during a second visit within 30 days. However, this could not be measured in 80% of the patients with severe disease, either because of safety reasons, or because international standards could not be met[17]. Therefore methacholine challenge tests were not interpreted in the present study.
Patients fulfilled questionnaires that assessed demographic data, medical history and medication use, as well as the Asthma Control Questionnaire (ACQ)[18], the Asthma Quality of Life Questionnaire (AQLQ)[19] and the Sino-Nasal Outcome Test-22 (SNOT-22)[20]. Physiologic testing of lung function included pre- and postbronchodilator spirometry, carbon monoxide

diffusion capacity, body plethysmography and, if possible, bronchial hyperresponsiveness to methacholine[17;21-23]. Atopic status was assessed by specific and total IgE a panel of common aero- and foodallergens (house dust mite, grass and birch pollen, herbs, molds and cat and dog dander, milk, soy, cod, peanut, ovalbumin and wheat) by ImmunoCAP. Atopy was defined as a score of > 0.35 kU/L for at least one of the specific IgE. Inflammatory status was assessed by exhaled nitric oxide[24], assessment of blood neutrophils, blood eosinophils and induced sputum cell differentials[25.26].

Variables

Age of asthma onset was defined as the age at which a physician had diagnosed asthma for the first time and asthma duration was calculated as the number of years since diagnosis. One packyear of cigarette smoking was defined as smoking 20 cigarettes a day for a one year. Patients had a positive history of nasal polyposis if it was diagnosed by an ENT-specialist and treated accordingly. Chronic use of oral corticosteroids (OCS) was defined as the daily use of OCS in the previous 3 months. The number of exacerbations was defined as the amount of prednisone bursts needed to control increased asthma symptoms in the past 12 months. Lastly, to allow inclusion of (ex)smoking asthmatics as well as asthmatics with "fixed' airflow limitation, we only excluded patient with "pure" COPD, defined as patients with a smoking history of >10 packyears with persistent airflow obstruction (FEV_1/FVC <0.7) and less than 12% improvement in FEV_1 after 400 mcg of inhaled salbutamol(27).

Statistical analysis

Non-normally distributed data were log transformed before initial analysis. For comparison between groups X^2- tests were used for proportions and unpaired t-tests for normally distributed variables. Factors associated with severe asthma were assessed by univariate and multivariate logistic regression analyses, with age, gender and asthma duration as co-variate. All analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL) or GraphPad Prism 5.0. P-values <0.05 were considered statistically significant.

RESULTS

A total of 200 patients with late onset asthma were selected of which 78 patients had severe asthma according to the international consensus criteria[15] and 98 had mild-moderate persistent asthma according to the GINA guidelines (table 1). Therefore a total 176

Table 1 Patient Characteristics

	Mild-moderate persistent N=98	Severe N=78	p-value
Age (yr)*	53.6 (11.4)	54.4 (9.8)	0.6
Gender (% female)	59.2	61.5	0.7
Age of onset*	41.8 (13.8)	40.2 (11.9)	0.4
Asthma duration†	9 (3-18.5)	10 (5-21)	0.07
Race caucasian (%)	82.7	87.2	0.4
(ex)smoker (%)	33.7	47.4	0.08
Packyears†	0 (0-4.5)	0 (0-7.6)	0.3
Total IgE Ku/L†	77.5 (26.3-277)	112 (51.7-325)	0.1
Atopy (positve RAST) (%)	52	34.6	0.02
IgE against Aspergillus spp (%)	10	9	0.7
Family history of atopy (%)	36.6	27.6	0.2
Family history of asthma (%)	34.4	38.2	0.6
BMI (kg/m2)†	27.3 (24.5-29.9)	28.6 (24.8-31.6)	0.2
Nasal polyposis (%)	26.5	53.8	<0.001
History of NSAID sensitivity(%)	11.2	16.7	0.4
SNOT-score*	1.15 (0.76)	1.4 (0.86)	0.02
Use of nasal corticosteroids (%)	45	74.4	<0.001

† Median (interquartile range) * Mean (SD)

participated in the study. More than half of the patients with severe asthma (59%) used oral corticosteroids on a daily basis, and 11.5% were on anti-IgE treatment.

Differences between patients with severe and mild-moderate asthma

As expected, patients with severe asthma consulted their treating physician more often, paid more visits to the ER, were more often hospitalized, and more often admitted to ICU than patients with mild-moderate asthma (Table 2).

Demographic characteristics, smoking, atopy and co-morbidities

As compared to the patients with milder disease, patients with severe late onset asthma did not differ with respect to age, age of asthma onset, or asthma duration. Also the female/male ratio was not different between patients with severe and mild-moderate asthma. However, patients with severe late onset asthma were less often sensitized to common allergens (52 vs 34%), had more nasal symptoms (higher SNOT score) and had more often a history of nasal polyposis (54 vs 27%), (Table 1; fig. 1).

Table 2. Symptoms, medication use and health care utilisation

	Mild-moderate persistent N=98	Severe N=78	p-value
ACQ-score*	1.17 (0.94)	1.91 (0.98)	<0.001
AQLQ-score*	5.4 (1.28)	4.8 (1.15)	0.002
Dose ICS, (fluticason eq.) †	500 (250-500)	1000 (1000-1500)	<0.001
OCS (%)	0	59	<0.001
Anti-IgE (%)	0	11.5	0.001
Exacerbations (%)			<0.001
- 0	70	17	
- 1-2	18	32	
- >3	12	51	
Doctors visits (%)			<0.001
- 0	14	0	
- 1-2	65	22	
- >3	21	78	
ED-visits (%)			0.04
- 0	90	75	
- 1-2	8	17	
- >3	2	8	
Hospitalisations (%)			0.003
- 0	93	74	
- 1-2	5	22	
- >3	2	4	
ICU-admissions (%)			0.01
- 0	99	86	
- 1-2	1	10	
- >3	0	1	

† Median (interquartile range) * Mean (SD)
ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ED, emergency department; ICU, intensive care unit. Exacerbations, doctors visits, ED-visits, hospitalisations are defined as the number of events in the past 12 months. ICU-admission are the number of admissions ever on the ICU.

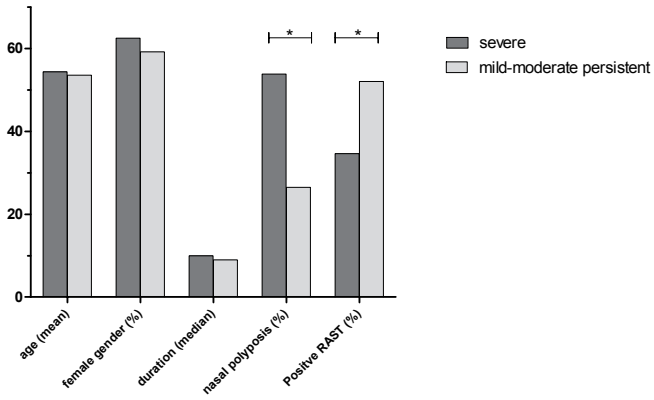


Figure 1. Age, gender, asthma duration, prevalence of nasal polyposis and atopy in patients with severe adult-onset asthma and mild-moderate persistent adult-onset asthma. *: p<0.05

Pulmonary function

Post bronchodilator (pb) FEV_1 and $pbFEV_1$/FVC ratio were lower in patients with severe late onset asthma than in mild-moderate asthma (82.4 vs 97.3 % and 80.4 vs 93.5 %, respectively). Post bronchodilator RV/TLC ratio was higher in patients with severe asthma (98.6 vs 88.1 %), suggestive of relatively more air trapping (Table 3).

Table 3. Lung function parameters

	Mild-moderate persistent N=98	Severe N=78	p-value
pbFVC,% pred*	107.2 (15.9)	104.2 (19.2)	0.3
pbFEV1,% pred*	97.3 (18)	82.4 (20.6)	<0.001
pbFEV1/FVC ratio %pred*	93.5 (13.1)	80.4 (16)	<0.001
pbRV/TLC, ratio %pred*	88.1 (15.8)	98.6 (21.8)	0.001
KCO, %pred*	99.6 (15.1)	102.4 (15.8)	0.3

* Mean (SD)

Pb, postbronchodilator; FVC, Forced Vital Capacity; FEV_1, Forced Expiratory Volume in one second; RV, Rest Volume; TLC, total Lung Capacity; KCO, Transfer coefficient expressing carbon monoxide diffusing capacity

Inflammatory markers

Patients with severe asthma showed more evidence of systemic inflammation, given the higher levels of blood eosinophils as compared to patients with milder disease (table 4). With respect to markers of airway inflammation patients with severe asthma had higher levels of sputum eosinophilia (median 11.6% vs. 0.8% resp. p = <0.001) as compared to patients with mild to moderate asthma (fig. 2). With respect to sputum neutrophils, no significant differences were found (73.5% vs 67.2% resp, p = 0.9).

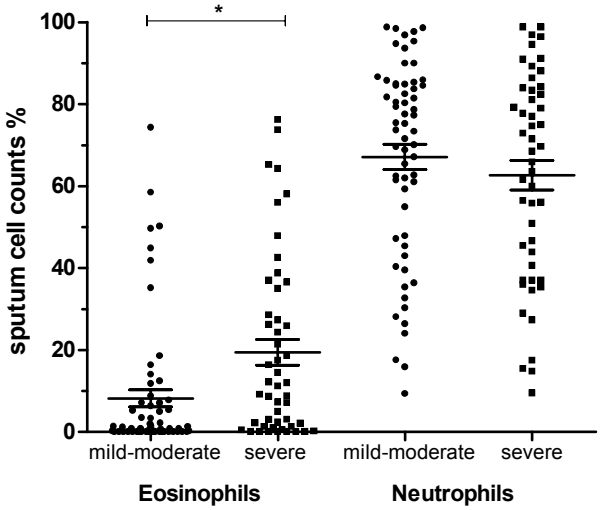
Table 4. Inflammatory markers

	Mild-moderate persistent N=98	Severe N=78	p-value
Blood eosinophils,109/l†	0.18 (0.09-0.31)	0.25 (0.14-0.5)	0.05
Blood neutrophils,109/l†	4 (3.1-4.9)	5.3 (3.9-6.8)	<0.001
FeNO (ppb)†	27 (16-50)	38 (19-73)	0.02
Sputum eosinophils %† (n=110)	0.8 (0.1-7.1)	11.6 (1.5-33.4)	<0.001
Sputum neutrophils %† (n=110)	73.5 (46.7-84.9)	67.2 (37.9-83.2)	0.9

† Median (interquartile range)

FeNO, Fractional exhaled Nitric Oxide

Figure 2. Percentage of sputum eosinophils and neutrophils in patients with severe and mild-moderate persistent adult-onset asthma. *: p<0.05



Factors associated with asthma severity.

When looking for factors associated with severe asthma, univariate logistic regression analyses showed significant associations between severe asthma and absence of atopy (OR = 2.0, p = 0.02), nasal polyposis (OR = 3.2, p = <0.001), blood neutrophils (OR = 7.6, p = <0.001), exhaled nitric oxide (OR = 1.5, p = 0.02) and sputum eosinophils (OR = 1.4, p = <0.001) (Table 5). When forcing all significantly associated variables into one model with age, gender and asthma duration as co-variates, multiple logistic regression analyses showed blood neutrophils (B = 2.4, p = 0.002, OR 10.9, 95%CI 2.4-51.0) and sputum eosinophils (B 0.4, p = 0.005, OR 1.5 95%CI 1.12-1.9) to be independently associated with severe late onset asthma and an almost significant trend was found for nasal polyposis (B1.12, p = 0.05, OR 3.0, 95%CI 0.98-9.6).

DISCUSSION

This study shows that adults with severe asthma that started in adulthood are mostly nonatopic, have persistent eosinophilic airway inflammation and higher blood neutrophils. As compared to patients with mild late onset asthma they had more nasal symptoms and nasal polyposis, increased exhaled nitric oxide levels, higher blood neutrophils and sputum

Table 5. Odds ratio's for factors potentially associated with severe late onset asthma.

	OR	95%-CI		p-value
		Lower	Upper	
Blood neutrophils	7.6	2.9	19.8	<0.01
Nasal polyposis	3.2	1.7	6.1	<0.01
Absence of atopy	2.0	1.1	3.8	0.02
FeNO (ppb)	1.5	1.1	2.2	0.02
Sputum eosinophils	1.4	1.2	1.7	<0.01
Blood eosinophils	1.3	0.98	1.8	0.06
Positive smoking history	1.8	0.96	3.3	0.07
Asthma duration	1.3	0.97	1.8	0.08
Familial asthma	1.2	0.62	2.2	0.6
Gender	1.1	0.6	2.0	0.8
Age of asthma onset	1.0	0.98	1.0	0.4
Age	1.0	0.98	1.0	0.6
BMI	1.0	0.98	1.1	0.3
Sputum neutrophils	1.0	0.62	1.6	0.9
IgE against food	0.9	0.27	2.9	0.8
Aspergillus	0.9	0.31	2.4	0.8
Race	0.7	0.3	1.6	0.4
Familial atopy	0.6	0.34	1.3	0.2

Odds ratio's from the univariate regression analyses.
OR, Odds Ratio; CI, Confidence Interval; FeNO, Fractional exhaled Nitric Oxide; BMI, Body mass index.

eosinophilia despite treatment. Gender, age of asthma onset, asthma duration, body mass index and sputum neutrophil counts were similar in patients with severe and non-severe disease. These results suggest that severe late onset asthma has a different underlying pathophysiological mechanism as compared to milder forms of late onset asthma, and may require a different therapeutic strategy.

The present study focused exclusively on patients with late onset asthma and showed that severe disease in these patients is associated with active airway inflammation that extends from the nose and sinuses to the peripheral airways. Moreover, elevated eosinophil counts in peripheral blood point towards a systemic component of the inflammatory process. This contrasts with patients with mild late onset asthma, and extends a previous study showing that, compared to patients with early onset asthma, those with severe late onset asthma had higher numbers of airway eosinophils and were less often sensitized to aeroallergens[28]. Our data fit in with the observation that amongst patients with difficult-to-control asthma persistent sputum eosinophilia was associated with late onset disease, absence of atopy, extensive sinus disease, and persistent airflow limitation[29]. Similarly, a cluster analysis

in asthma patients referred to secondary care, revealed a cluster of severe eosinophilic asthmatics who had more often late onset of their disease[2]. Together, these data point towards a distinct adult late onset severe asthma phenotype, characterized by absence of allergic sensitization, presence of nasal polyposis and high eosinophil counts in blood and sputum.

In the present study we found more females than males with late onset asthma, however female gender was not related to disease severity. This is in contrast with other studies comparing mild and severe asthma in general, showing more severe disease in females[30,31]. Perhaps, hormonal factors are involved in the susceptibility of developing asthma in adulthood, but not in developing more severe disease[32].

We did not observe a difference in sputum neutrophils between mild-moderate and severe late onset asthma. This also contrasts with severe asthma in general, in which sputum neutrophilia is often associated with more severe disease[30,33]. This implies that sputum neutrophilia might be a characteristic of all late onset asthma, related to the trigger that initiated asthma in the first place, such as occupational sensitizers[34], viruses[7], atypical bacteria[35] or fungi[36]. Neutrophilia in peripheral blood did show an association with more severe late onset asthma, which, together with blood eosinophilia reflects the systemic nature of the disease.

Patients with severe late onset asthma were not different from those with non-severe asthma with respect to body mass index (BMI). This is surprising, since a high BMI is increasingly associated with onset of asthma in adulthood and also with more severe asthma[3;37;38]. One explanation might be that non-asthmatic obese adults might gradually develop (mild) asthma due to the pro-inflammatory effects of adipose tissue[39], whereas patients with severe disease might become obese as a consequence of the use of oral corticosteroids. Thus, a high BMI might be associated with mild as well as severe asthma, via different mechanisms.

The strength of our study lies in the criteria we used to define severe asthma. This definition was based on international consensus that was obtained amongst experts in severe asthma from tertiary referral centres, academia, patient organisations and pharmaceutical industry[15]. The definition was based on symptoms of uncontrolled asthma despite the correct and regular use of high doses of inhaled or chronic oral corticosteroids combined with long-acting bronchodilators and other controllers. By using these stringent criteria of asthma severity in patients with late onset disease, we identified a rather homogeneous phenotype of patients with persistent eosinophilic upper and lower airways inflammation. This illustrates

that using a strict definition of severe asthma helps in identifying the category of patients that is resistant to current asthma therapy and requires novel anti-inflammatory biologicals.

In conclusion, we showed that patients with severe late onset asthma have predominately non-atopic eosinophilic airway inflammation with nasal polyposis as compared to patients with mild-moderate persistent disease. In addition, increased sputum eosinophils and blood neutrophils are independently associated with more severe disease, irrespective of age, gender and asthma duration. These results suggest that severe late onset asthma represents a specific phenotype with different underlying pathophysiology as compared to milder disease, but also as compared to severe asthma in general. The next step in research should include prospective follow-up studies with a focus on causative mechanisms and early predictors of severe late onset disease in order to, eventually, prevent the development of severe asthma in adulthood.

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Chapter 5

Chronic rhinosinusitis: predictor of lower airway inflammation in newly diagnosed late-onset asthma

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(Submitted)

INTRODUCTION

Asthma is a complex disorder that includes distinct subtypes, potentially with different aetiologies, natural histories and responses to treatment[1-3]. The classical type of asthma is associated with atopy, starts early in childhood and typically runs in families[4,5]. This type of asthma has been extensively studied in in vivo and in vitro asthma models, and can be reasonably well controlled by current anti-asthma medications[6]. In contrast, asthma that starts in adulthood represents a different clinical phenotype. Studies have shown that it is often more severe[7,8] and less responsive to therapy[9]. Previous studies in patients with asthma from our group showed that it's more often associated with fixed airflow limitation[10], in particular in non-atopic males[11]. The pathogenesis and pathophysiology of late-onset asthma are poorly understood[12].

Rhinitis has been shown to be a significant risk factor for late-onset asthma in both atopic and non-atopic patients[13,14]. Patients with rhinitis with persistent and severe nasal symptoms and a personal history of physician-confirmed sinusitis have an additional increased risk of asthma development[15-18]. The link between nasal polyps and adult-onset asthma is even stronger[16,17]. Histopathologic features of chronic rhinosinusitis (CRS) and lower airways inflammation asthma largely overlap[16,19]. This was also confirmed in patients with severe asthma in whom a relationship between sinonasal mucosal thickness and bronchial inflammation was found, particularly in those with late-onset disease[20].

The prevalence of chronic rhinosinusitis (with or without nasal polyps) at asthma onset in adults is not known, nor is it known whether there is a link between CRS and inflammation in the lower airways in the early stages of the disease.

The aim of the present study was therefore to assess the frequency of CRS (including nasal polyposis) in newly diagnosed late-onset asthma, and to test the hypothesis that the severity of chronic rhinosinusitis (symptoms and radiologic/endoscopic signs) and presence of nasal polyps in these patients is related to the severity of lower airway inflammation as assessed by the percentage of eosinophils in induced sputum and the fraction of exhaled nitric oxide (FeNO).

METHODS

Patients

Patients older than 18 years with recently diagnosed (<1 year) asthma were recruited from one academic and two non-academic pulmonary second line referral outpatient clinics. One of the two non-academic pulmonary clinics had an agreement with the General practitioners in the area to refer al patients with symptoms suggestive for asthma. These patients are therefore considered as primary care population. The diagnosis of asthma was confirmed by reversibility in $FEV_1 \geq$ 12% of the predicted value or hyperresponsiveness to inhaled methacholine (PC_{20} < 8mg/ml). Patients were excluded if they had a prior diagnosis of asthma as an adult or reported any symptom or sign of asthma during childhood, including a doctor's diagnosis of "asthma" or "bronchitis" before the age of 18, or use of bronchodilator medication during childhood, or frequent episodes of dyspnea during childhood associated with absenteeism from school. Smokers or ex-smokers with a smoking history > 10 packyears were excluded if they did not show an improvement in FEV_1 of at least 12% after inhalation of 400 µg salbutamol with a normal diffusion capacity at the time of inclusion. At the time of the study visit, patients had had no symptoms of respiratory infection for at least 4 weeks. The study was approved by the local Hospital Medical Ethics Committee and was registered in the Netherlands trial register under NTR 1846. All patients gave their written informed consent.

Design

The study had a cross-sectional design. During one hospital visit lung function was measured, sputum was induced and peripheral blood was taken. Then symptoms of CRS were evaluated and sinus CT-scanning and nasal endoscopy were performed.

Assessment of CRS

CRS was defined according to the European Position Paper on Rhinosinusitis and Nasal polyps (EP3OS) based on the following criteria[17] :

a. Symptoms of CRS:
   Presence of more than two symptoms of CRS (based on SNOT-22 questions 4, 5, 6 and 12 using a cut-of point of ≥2 ("mild or slight problem" and worse)) for at least 12 weeks: 1.nasal blockage, obstruction or congestion or 2. nasal discharge (either anterior or posterior nasal drip) or 3. facial pain or pressure or 4. reduction or loss of smell, and EITHER
b. Radiologic signs of CRS:

Sinus CT-scan abnormalities defined as a Lund-Mackay score ≥ 4[21-23] OR

c. Endoscopic signs of CRS/nasal polyps:
Endoscopic signs of CRS such as mucopurulent discharge in the middle meatus, and/ or edema or obstruction in middle meatus (scored by nasal endoscopy as absent or present)[24] or nasal polyps were scored as absent or present.

Based on these criteria patients were divided into three groups: patients with CRS with nasal polyposis (CRSwNP), patients with CRS without nasal polyposis (CRSsNP) and patients without CRS.

Symptoms of CRS were scored using the Sino-Nasal Outcome test-22 (SNOT-22)[25]. Sinus CT-scans were scored by a radiologist according to the validated Lund-MacKay scoring system[23] with scores ranging from 0 to 24.

Nasal endoscopy was performed by a rhinologist using 2.7 mm rigid 30° endoscopes. Endoscopic signs for chronic rhinosinusitis were defined, based on a standardised scorings system as described previously[24]. In short, meatus/ concha inferior and meatus medius were checked for watery edema/congestion (scored 0-2), rhinorrhea (scored 0-2), scars/adhesions (scored 0-2) and crusts (scored 0-2). A total score of 0-32 is possible, and each side was scored separately (0-16).

Sputum induction and processing

Sputum induction, processing and analysis were performed according to previously validated methods[26]. Prior to sputum induction, patients inhaled 400µg salbutamol. Sputum was induced by inhalation of NaCl 4.5% during 3x5 min intervals using a high output nebulizer [KLAVAmed, Bielefeld, Germany]. Whole sputum samples were processed according to international recommendations[26]. Sputum samples containing > 80% squamous cells were labelled as not-interpretable and excluded from analysis. Differential cell counts were expressed as the percentage of non-squamous cells. Sputum eosinophilia was defined as eosinophilis ≥3%[27]. Sputum counting was performed by one experienced and qualified technician blinded to the clinical details.

Spirometry

Spirometry (MasterscreenPneumo; Jaeger; Würzburg, Germany) was performed by a trained respiratory technician according to the latest recommendations[28]. Measurements were performed after withholding short and long-acting bronchodilators for at least 8 hrs. Reversibility in FEV_1 was measured as change in FEV_1, expressed as percentage of the predicted value, 10 min after inhalation of 400µg inhaled salbutamol.

Allergy testing

Atopic status was assessed by specific IgE to a panel of common aeroallergens (house dust mite, grass and birch pollen, herbs, molds and cat and dog dander) by ImmunoCAP. Atopy was defined as specific IgE > 0.35 Ku/L for at last one of the tested allergens

Fraction of exhaled nitric oxide (FeNO)

FeNO level was measured with a portable rapid-response chemoluminescent analyser (flow rate 50mL/s; NIOX System, Aerocrine, Sweden) according to recent guidelines[29].

Statistical analysis

Non-normally distributed data were log-transformed for further analysis. Variables were summarized by descriptive statistics. For comparisons of proportions between groups, chi-square test were used. Student's t-test and one-way analysis of variance (ANOVA) was used when normality and variance equality were confirmed and with Wilcoxon and Kruskal-Wallis test otherwise. Bonferroni correction was used for post hoc multiple comparisons. Univariate analysis was performed using Pearson's correlation test to indentify factors associated with the severity of lower airways inflammation (percentage of eosinophils in sputum or FeNO level).
Multiple regression analysis with factors significantly associated with lower airways inflammation was performed including age, gender, atopic status and blood eosinophil count.

RESULTS

Three-hundred fifty-eight adult patients with recently diagnosed asthma were asked to participate in the study, and 200 agreed [Figure 1]. There were no differences between participants and non-participants with respect to age (p=0.23), atopic status (p=0.5), postbronchodilator FEV_1 (p=0.75) or bronchial hyperresponsivess to methacholine (p=0.43). The included patients were significantly more often males than females (p=0.02) and had more often a Caucasian ethnic origin (p<0.001) as compared to the non-responders.
The patient characteristics of the patients included in the study are presented in Table 1.

Figure 1: Flow chart
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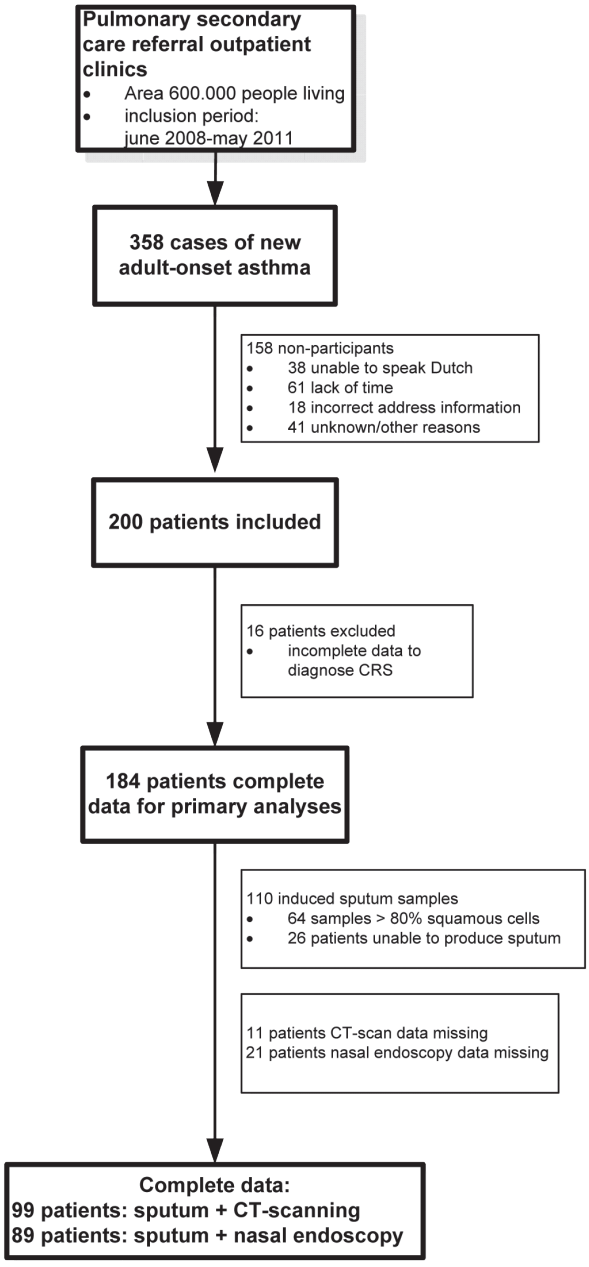


Frequency of CRS in newly diagnosed asthma in adults

Among the 200 included adults, 193 patients fully completed the SNOT-22 questionnaire. Sinus CT-scanning was performed in 186 patients and nasal endoscopy was performed in 163 patients [Figure 1]. In 184 patients enough data were available to make a diagnosis of CRS according to EPOS criteria, and CRS was confirmed in 100 patients (54%). Thirty-six patients (20%) had CRSwNP and 64 patients (35%) had CRSsNP. In the total population, 54 patients (27%) used nasal corticosteroids. The results are presented in Table 1.

Association between severity of CRS and severity of lower airways inflammation

Induced sputum samples were obtained in 174 patients. However, samples from 64 patients did not meet the minimum quality criteria (<80% squamous cells in the cell differential count).Thus, induced sputum data from only 110 patients were analysed. Among the 110 patients who successfully produced sputum, 99 patients underwent sinus-CT-scanning and in 89 patients nasal endoscopy was performed [Figure 1].

Table 1. Patient characteristics

	n=200
Gender (% female)	56
Age (years) *	48 ± 14.9
BMI *	28 ± 5.3
Caucasian ethnicity, %	83
Smoking history (py) #	3 (0-14)
Aspirin sensitivity, %	unknown**
Inhaled corticosteroids, %	80
Dose ICS, µg/day #	250 (250-500)
Antihistamines, %	11
Leukotriene receptor agonists, %	5
Atopy (% positive RAST)	44
Nasal corticosteroids, %	29
symptoms of CRS, %1	60
CRS according to EP3OS criteria, %1	54
CRSsNP, %	34
CRSwNP, %1	20

* mean/SD; # median (interquartile range); [1] Defined by EP3OS criteria (17).
** aspirin is not a popular pain killer in the Netherlands; people prefer acetaminophen
CRSsNP= Chronic rhinosinusitis without nasal polyps; CRSwNP= Chronic rhinosinusitis with nasal polyposis; ICS= inhaled corticosteroids; Dose ICS= fluticason equivalent; py= pack years.

The sinus CT-scan-score (n=99) correlated significantly with the percentage of eosinophils in sputum and the level of FeNO (r=0.57, p< 0.001 and r=0.50, p<0.001, respectively; Figure 2). Furthermore, the nasal endoscopy score for CRS (n=89) correlated significantly with the percentage of sputum eosinophils and level of FeNO (r=0.21, p=0.04 and r=0.30, p=0.004).
The percentage of sputum eosinophils was significant higher in patients with CRSwNP, as compared to patients with CRSsNP or patients with only asthma (p<0.05 and p=0.02; Figure 3). In line, patients with CRSwNP had a higher FeNO level, as compared to patients with CRSsNP or patients with only asthma (p<0.02 and p=0.001).
No significant correlation was found between the sinonasal outcome score (SNOT-22 questionnaire) and percentage of sputum eosinophils or FeNO-level (p=0.57 and p=0.07).

Figure 2: Correlation between the sinus CT scan score and the percentage of sputum eosinophils (left) and FeNO level (right) in patients with late-onset asthma

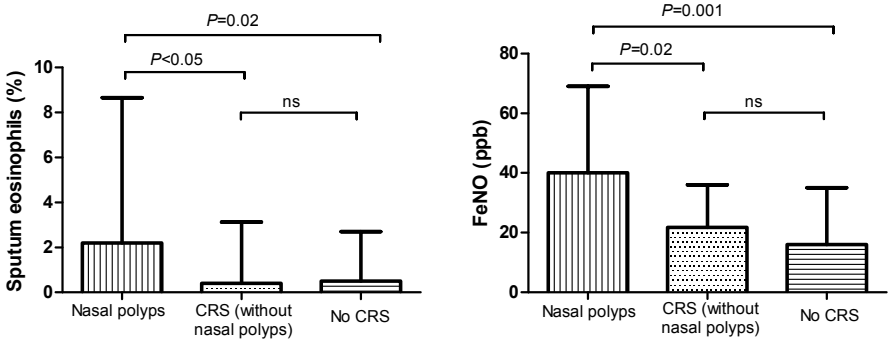
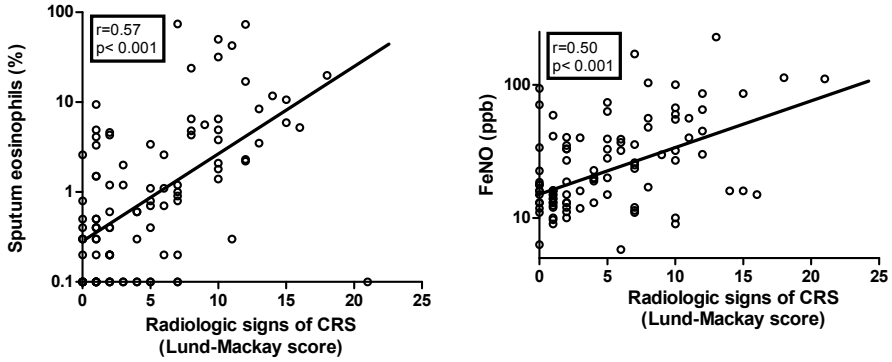


Figure 3: Histogram showing group comparison for percentage of sputum eosinophils (left) and FeNO level (right) as geometric mean [95% confidence interval]



Multivariate analysis

Multivariate regression analysis including sinus CT-scan score, nasal endoscopy score, the presence of nasal polyps, as well as blood eosinophil counts, age, gender and atopic status showed that the sinus CT-scan score (P<0.001) and blood eosinophil counts (p<0.001) were independently associated with sputum eosinophilia (correlation r=0.70, r^2=49%; p<0.001; Table 2). Repeating the analysis with FeNO level as dependent variable showed that the sinus CT-scan score (p<0.05), male gender (p=0.04) and positive atopic status (p=0.002) (correlation r=0.68, r^2=47 %; p<0.001) were independent determinants of increased FeNO level.

Table 2 Multiple regression analysis. Factors independently associated with the percentage of sputum eosinophils (n=110).

	B	SE	p value	95% CI
Sinus CT-scan score	0.35	0.04	<0.001	0.06-0.198
Nasal endoscopy score	0.10	0.04	0.25	-0.033-0.124
Nasal polyps	0.03	0.41	0.79	-0.701-0.915
Blood eosinophilic count*	0.45	0.17	<0.001	0.505-1.181
Age (years)	0.05	0.01	0.59	-0.03-0.017
Male gender	0.00	0.32	0.99	-0.631-0.629
Positive atopic status	0.05	0.30	0.59	-0.443-0.768

* Values logarithmically transformed to achieve normality before analysis; B= β coefficient; SE= standard error; CI= confidence interval

DISCUSSION

This study shows that more than half of patients with a recent diagnosis of late-onset asthma have chronic rhinosinusitis according to the EP3OS criteria[17] and 20% have nasal polyposis. Patients with nasal polyposis have higher percentages of eosinophils in sputum as compared to patients without nasal polyposis. The severity of chronic rhinosinusitis, as assessed by sinus CT-scan score is independently associated with the percentage of eosinophils in induced sputum and the level of FeNO. This suggests that chronic rhinosinusitis in adults may be an early indicator of late-onset eosinophilic asthma.

The present study identifies chronic rhinosinusitis (including nasal polyposis) as an important presenting characteristic of patients with newly diagnosed late-onset asthma. This fits in with the 'united airway disease concept' in a specific subpopulation of patients whose asthma started in adulthood, showing a high prevalence of 54% of confirmed CRS and of 20% of CRSwNP in these patients versus only 10.9% and 4% of the normal population, respectively[17,30]. The results confirm and extend findings form earlier studies showing CRS to be an important

co-morbid condition in patients with asthma, that is associated with late onset disease[31] and with greater disease severity[20,23,33]. Not only was the frequency of CRS and CRSwNP high in our patients with newly diagnosed asthma, but patients with sinus disease also featured more severe airway inflammation, as assessed by eosinophils in induced sputum and level of FeNO. Together, these data point towards an association between chronic rhinosinusitis, nasal polyposis and onset of asthma in adulthood.

The pathophysiological mechanisms underlying the association between sinus disease and lower airway inflammation are not completely understood1[6,19]. Cytokine patterns in sinus mucosa from patients with CRS highly resemble those in bronchial mucosa from patients with asthma[34]. Eosinophils have been shown to be the dominant cell type in both nasal and broncho-alveolar lavages in patients with CRS and co-morbid asthma[35]. One factor that might have contributed to upper and lower airway inflammation is Staphylococcal exotoxin as sensitising factor or as superantigen[36,37]. This was recently suggested by Bachert and colleagues[38] who showed that eosinophilic inflammation in patients with CRSwNP and co-morbid asthma is associated with the formation of IgE antibodies against Staphylococcus aureus enterotoxin[38]. This suggests that colonization of the paranasal sinuses with this pathogen might elicit an "intrinsic" IgE response, with subsequent eosinophilic inflammation of the airway mucosa. Another explanation might be related to the expression of transforming growth factor-beta 1 (TGF-ß1)[39,40]. TGF-ß1 represents a master switch in inflammation and remodelling processes in both upper and lower airways and might provide a key for understanding inflammation and remodelling. The key question is whether inflammation of the upper and lower airways in patients with late onset asthma are causally related. The observation that CRS is highly prevalent in the earliest stages of late onset asthma and that the extent of upper airway inflammation is associated with the intensity of inflammation in the lower airways does suggest such a causal link. If so, eosinophilic CRSwNP might be regarded as an early predictor of the eosinophilic asthma phenotype[41].

Our study may have some limitations. First, the diagnosis of late onset asthma was based on the absence of respiratory symptoms in childhood. Despite careful attempts to avoid recall bias, we cannot exclude this entirely. However, if airway disease was present during childhood, it was apparently not severe enough to be remembered. Second, we could not obtain adequate sputum in all patients. However, no significant differences were found in severity of chronic rhinosinusitis between the patients who successfully produced sputum and those who did not (data not shown). Therefore, we do not believe that the results of our study are biased by these limitations.

The present study has clinical implications. Late onset asthma is an underexposed and often misdiagnosed respiratory condition[42]. The presence of CRS, in particular if associated with nasal

polyposis should be a warning sign for physicians that late-onset asthma might be imminent. Alternatively, patients with a recent diagnosis of late-onset asthma should be screened by an allergist or if necessary by an ENT specialist for CRS and nasal polyps. This is important, since studies have shown that treatment of CRS and nasal polyposis may improve asthma control[43].

In conclusion, this study shows that CRS and nasal polyposis are highly prevalent in newly diagnosed late-onset asthma and that the severity of CRS in these patients correlates with the intensity of eosinophilic inflammation in the lower airways. This suggests a pathogenetic link between chronic sinus disease and the eosinophilic asthma phenotype. Whether CRS or nasal polyposis at asthma onset predicts a more severe course of the disease with worse long-term prognosis needs to be confirmed in prospective long-term follow-up studies.

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Chapter 6

Non-atopic males with adult-onset asthma are at risk of persistent airflow limitation

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INTRODUCTION

Asthma is a heterogeneous condition with many clinical subtypes differing in severity, natural history, and response to therapy[1]. The classical, most prevalent type of asthma is associated with atopy, starts in early childhood, and typically runs in families[2,3]. This type of asthma has been extensively studied in in vivo and in vitro asthma models, and can be reasonably well controlled by current anti-asthma medications[4].

There are, however, many other phenotypes of asthma, in particular in adults, that have received less attention. These phenotypes often have no evidence of atopic disease or allergic sensitization[5], present with a negative family history, and typically report the onset of their asthma in adult life[3,6]. Adult-onset asthma is still poorly understood, and mechanisms have never been investigated systematically. Some studies have shown that it is often severe at onset[7], less responsive to therapy[8] and more likely to persist[7]. Cross-sectional and population based studies in patients with severe and non-atopic asthma have shown that those with adult-onset disease are also more prone to develop persistent airflow limitation[9-11]. Hence, adult-onset asthma represents a population of major interest with regard to the risk factors of accelerated loss of lung function as observed in asthmatics as compared to controls[12].

Recently, two subtypes of adult-onset asthma have emerged after applying cluster analysis to a large database of patients with asthma[13]. One consisting mainly of obese women with high symptoms scores and little airway inflammation, and one consisting of more males with intense airway inflammation, low symptom scores and persistent airflow limitation. An adult asthma phenotype of obese women was confirmed by cluster analysis in another large database of patients with asthma, and these patients were characterized by less atopy and reduced FEV_1[14].

We questioned whether obesity, male or female gender, and absence of atopy might be risk factors of persistent airflow limitation in patients with adult-onset asthma.

Therefore, the aim of the present study was to investigate whether these and six other potential risk factors (age, age of asthma onset, asthma duration, smoking history, race, and use of oral corticosteroids) were associated with persistent airflow limitation in patients with the adult-onset asthma phenotype.

METHODS

Patients

Consecutive secondary referral centre patients with adult-onset asthma visiting the outpatient clinic of the Academic Medical Centre between October 2008 and October 2009

entered this study. Patients were eligible if they had a physician's diagnosis of asthma onset after the age of 18 years. A diagnosis of asthma was defined by a history of episodic dyspnea and wheezing, and documented reversibility in FEV1 of greater than 12% of the predicted value, or hyperresponsiveness to inhaled methacholine chloride (PC20 < 8.0 mg/ml) in the past 5 years. Patients with a history of childhood dyspnea attacks (spontaneous or during exercise), a childhood doctors' diagnosis of asthma or chronic bronchitis, or childhood use of pulmonary medication were excluded, as were patients with other pulmonary diseases or non-related major co morbidities.
Current and ex-smoking was allowed only if the patient had normal diffusion capacity and a > 12% improvement in FEV_1 after inhalation of 400 mcg of salbutamol at the time of inclusion1[5]. The study was approved by the hospital Medical Ethics Board and all patients provided written informed consent (MEC 08/358).

Design

In this cross sectional study all patients underwent several measurements to identify factors that could be associated with lung function decline, including a standard questionnaire, physical examination, allergy testing and pre and post bronchodilator spirometry.

MEASUREMENTS

Questionnaire and physical examination

The questionnaire included demographic data, age at asthma onset, duration of asthma, severity of asthma symptoms, smoking history and medication use. Physical examination included weight, height, assessment of co-morbidities and signs of any other disease.

Allergy tests

Atopic status was assessed by specific IgE to a panel of common aeroallergens (house dust mite, grass and birch pollen, herbs and cat and dog dander) by RAST or by a positive skin prick test to one of these allergens. Atopy was defined as a score of > 0.35 kU/L for at least one of the specific IgE's or by > 3mm wheal response.

Lung function testing

Spirometry was performed according to standard lung function technique(16) using spirometry (Masterscreenpneumo; Jeager; Wurzburg, Germany) by an experienced technician. Reversibility in FEV_1 was measured 10 min after administration of 400µg inhaled Salbutamol and was expressed as change in percentage predicted.

Analysis

Group differences were analyzed using unpaired students t-test and Chi-square analysis. Factors considered to be potentially associated with a lower FEV_1/FVC were age, gender, age of asthma onset, asthma duration, race, body mass index, number of smoking packyears, atopy and chronic use of oral corticosteroids. Age of asthma onset was defined as age at which the physician's diagnosis of asthma was established for the first time. Asthma duration was defined as the number of years since asthma onset. Number of smoking packyears was calculated by defining 1 packyear as smoking 20 cigarettes a day for a whole year. Chronic use of oral corticosteroids was defined as the daily use of oral corticosteroids in the previous 3 months before the study.

Potential risk factors were analyzed both as continuous and dichotomous independent variables, using the following contrasts: asthma duration ≥ 10 yr vs. < 10 yr (median for whole group); age ≥ 47 yr vs. < 47 yr (median for whole group); atopic vs. non-atopic; Caucasian vs. non-Caucasian Race; chronic use of oral corticosteroids vs. no use of oral corticosteroids, never smoker vs. (ex)-smoker and packyears ≥ 1 yr vs. 0 yr (median for whole group).

Linear regression was used to analyse the association between potential risk factors and FEV_1/FVC. Results were expressed as slope of the regression line (B) with 95% confidence interval (CI), which indicates the increase in the dependent variable per one unit increase in the independent variable. For further statistical analyses, subjects were divided into two groups for FEV_1/FVC ≥0.7 and <0.7 (median of the whole group). Logistic regression was used to estimate odds ratios with 95% confidence intervals for persistent airflow limitation. In addition, a full multiple logistic regression analysis was applied with all significant factors forced into the model. Analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). P-values less than 0.05 were considered statistical significant.

Sample size estimation

For multivariate prognostic analysis there is no formal way to calculate statistical power. However, the sample size was based on the requirement for the ratio of the number of

patients versus the number of predictors to be ten or higher[17]. Therefore, including eight predictors required at least 80 participants.

RESULTS

Comparison between patients with an FEV_1/FVC <0.7 vs. >0.7

88 patients with adult-onset asthma were included in this study. The median (range) age of the cohort was 47.6 (26-75) years, 51.7% was atopic and 58% of the cohort was female as shown in Table 1. Comparison between characteristics of patients with and without persistent airflow limitation is shown in Table 2. Patients with persistent airflow limitation were significant older, more often male, had a longer asthma duration, were less often atopic, were more often Caucasian, and were more often on chronic oral corticosteroids.

Table 1. Baseline characteristics of patients with adult onset asthma (N=88)

Age*	47.6	(11.7)
Gender (Female) %	58	
Age of onset (yr)*	36.8	(11.9)
Asthma duration (yr)†	10	(1-31)
Atopy %	51.7	
Asthma severity(35) %		
- Severe	58	
- Non severe	42	
Race (Caucasian) %	63.3	
BMI†	27	(18-45)
ex- smoker %	27.3	
Current smoker %	6.8	
Packyears†	0	(0-26)
ICS dose (µg/day) †	1000	(250-2000)
Chronic OCS use %	27.3	
Total IgE (n=73)†	161	(5-5295)
pbFVC %pred*	107.3	(18.2)
pbFEV1 %pred*	89.9	(17.5)
pbFEV1/FVC %pred*	109.0	(14.3)

* mean (SD) † median (range)
BMI, body mass index; ICS, Inhaled corticosteroids fluticasone equivalent; OCS, oral corticosteroids; pb, postbronchodilator; FVC, Forced Vital Capacity; FEV_1, forced expiratory volume in 1s

Table 2. Comparison of adult-onset asthma patients with or without persistent airflow limitation.

	pbFEV1/FVC ≥0.7 (n=45)		pbFEV1/FVC <0.7 (n= 43)		P-value
Age (y)*	43.2	(11.0)	53.5	(10)	< 0.001
Gender (Female) %	74.0		37.8		< 0.001
Age of onset (y)*	35.4	(11.2)	38.8	(12.7)	0.2
Asthma duration (y)†	7.9	(1-30)	13.7	(1-31)	0.03
Atopy %	65.3		35.8		0.004
Asthma severity(35) %					0.03
- Severe	40		67.7		
- Non severe	60		32.3		
Race (caucasian) %	54.0		74.4		0.03
BMI†	27.5	(19-45)	26.0	(18-42)	0.52
ICS dose (µg/day) †	500	(250-2000)	1000	(500-2000)	0.07
OCS use %	18.0		39.5		0.04
(ex)smoker %	26.0		44.7		0.052
Packyears†	0.0	(0-25)	0.0	(0-26)	0.08
pbFVC % pred*	102.8	(15.9)	112.7	(19.5)	0.001
pbFEV1 %pred*	95.9	(14.9)	80.0	(14.8)	0.003

* mean (SD) † median (range)

BMI, Body mass index; ICS, Inhaled corticosteroids fluticasone equivalent; OCS, oral corticosteroids; pb, post bronchodilator; FVC, forces vital capacity; FEV_1, Forced expiratory volume in 1s.

Association between FEV_1/FVC and associated characteristics.

Linear regression analysis showed a negative association for age (r = -0.43, B = -0.19, p = <0.01), asthma duration (r = -0.34, B = -0.02, p = 0.002), atopy (r = -0.31, B = -0.31 p =0.004), use of oral corticosteroids (r = -0.24, B = -0.26, p = 0.03), number of packyears (r = -0.24, B = -0.02, p = 0.03), Caucasian race (r = -0.23, B = -0.24, p = 0.03) and a positive association for male gender (r = 0.37, B = 0.37, p = <0.01) and BMI (r = 0.21, B = 0.02, p = 0.05) with FEV_1/FVC. There was no association with age of onset (p = 0.2). Multivariate regression analysis including all significant co-variates showed a negative association between post bronchodilator FEV_1/FVC and absence of atopy (r = -0.27, B = -0.26, p = 0.01) and a positive for male gender (r = 0.31, B = 0.30, p = 0.004) (table 3).

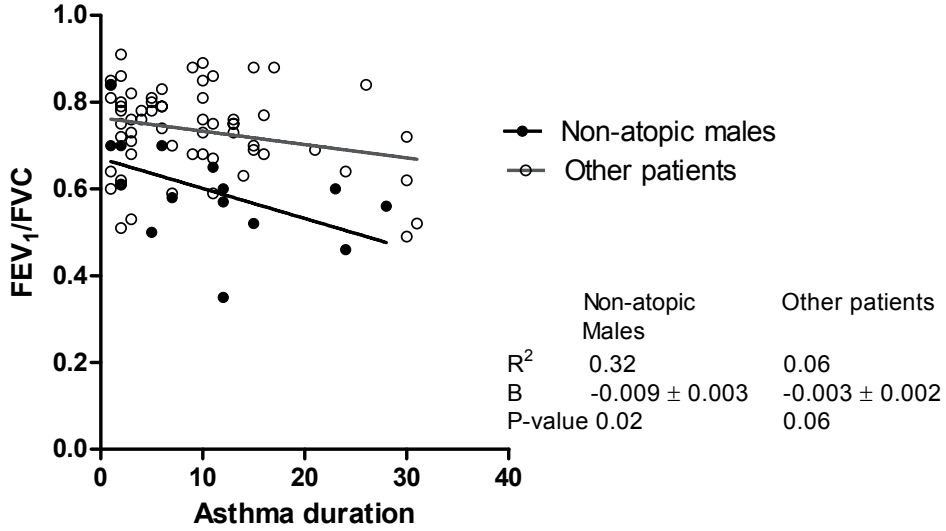
Logistic regression analysis showed that patients with a lower $FEV1_1$/FVC were 10.8 (CI: 2.6-45.2) times the odds to be male and 5.2 (CI: 1.3-20.3) times the odds to be non-atopic (table 3). To illustrate the magnitude of the changes in lung function in non-atopic males and the other patients with adult-onset asthma we calculated the "surrogate decline" in $FEV1_1$/FVC for the 2 groups by analysing the relationship between asthma duration and postbronchodilator $FEV1_1$/FVC ratio, shown as regression lines in Figure 1.

Table 3. Odds ratio's for factors potentially associated with FEV1/FVC <0.7

	OR	95% Confidence Interval		P-value
		Lower	Upper	
Male gender	10.8	2.61	45.24	0.01
Absence of atopy	5.18	1.32	20.29	0.02
Asthma duration > 10 y	4.16	1.02	16.90	0.05
Age > 47 y	3.21	0.85	12.05	0.08
OCS use	1.58	0.33	7.48	0.57
Caucasian race	1.16	0.30	4.49	0.83
Packyears > 10 y	0.00	0.00	0.00	0.90
BMI >27	0.04	0.9	1.2	0.52

Odds ratios from multivariate logistic analysis including all significant factors from the univariate analyses. OR, Odds ratio; OCS, oral corticosteroids.

Figure 1. Relationship between asthma duration (y) and postbronchodilator FEV_1/FVC in male non-atopic patients versus the other patients with adult-onset asthma



DISCUSSION

The present study shows that in patients with adult-onset asthma, male gender and absence of atopy are independently associated with persistent airflow limitation irrespective of age, smoking habits or body mass index. The present study confirms and extends previously published data by showing that non-atopic patients with adult-onset asthma are particularly at risk of developing persistent airflow obstruction[9-11].

Although more women presented with adult-onset asthma, which confirms previous findings[10], male gender was found to be an independent risk factor of persistent airflow limitation in the adult-onset asthma phenotype. Studies investigating the association between gender and decline in lung function have shown inconsistent results. Several studies have shown that young, mostly atopic females are at higher risk for developing more severe asthma[18] and for lung function decline[18,19], whereas other studies have shown no increased risk for decline in lung function in females[20]. In the TENOR study[21] males with asthma appeared to have and increased risk for persistent airflow limitation, independent of smoking habits and asthma duration. Absence of atopy as a risk factor of persistent airflow limitation has been found by one study showing an accelerated decline in lung function in patients with "intrinsic" asthma as compared to "extrinsic" asthma[20]. Our study shows that amongst patients with asthma that starts in adulthood, women are most prevalent, but males are at highest risk of developing persistent airflow limitation.

Obesity was not a risk factor for persistent airflow limitation in our study population. This seems to be in contrast with the results of the SARP study, showing an asthma phenotype characterized by obese women with late onset asthma and low postbronchodilator FEV_1[14]. However, in this latter study FEV_1 was analysed as an absolute value whereas in our study we used the ratio of FEV_1 and FVC, which may explain the difference in interpretation. Several studies have shown that obesity is inversely related to the severity of airway inflammation[22-24]. It is therefore plausible that obesity per se does not lead to loss of lung function, which is in agreement with our findings.

The mechanism underlying the association between male gender and persistent airflow limitation is not straightforward. It could be related to a genetic predisposition to develop persistent airflow limitation, or to environmental factors other than smoking. A genetic predisposition is a possibility, but until now there are no data to support in gene polymorphisms that are associated with persistent airflow limitation in males[19]. Environmental factors cannot be entirely excluded either, because we did not take a detailed occupational history from our patients, and thereby cannot judge the influence of potential harmful exposures in the past. However, exposure to occupational agents, including traffic related air pollution has been shown to be associated with increased risk for the development of adult-onset asthma[25-27], and therefore, a common cause of onset of asthma in adulthood and progressive decline in lung function could be a plausible explanation for our findings. Prospective studies taking ongoing occupational and environmental exposures in atopic and non-atopic males into account are needed to further explore this possibility.

In our study patients with allergic asthma were found to be less prone to develop persistent airflow limitation. This confirms earlier observations in patients with severe asthma, showing that only those with adult-onset non-atopic asthma had lower FEV_1 for a given duration of asthma[9]. It suggests that non-atopic asthma is a different disease with different predisposing factors and causal mechanisms, possibly related to infections with viruses[28], atypical bacteria[9] or fungi. Sensitiziation to fungi, in particular Aspergillus Fumigatus, has recently been described to be associated with persistent airflow limitation[29]. Unfortunately, our allergen panel did not include Aspergillus spp. Therefore, a proportion of our "non-atopic" patients might have been monosensitized to Aspergillus after all.
Taken together, the findings of our study raise novel hypotheses on mechanisms of airway remodeling that need further investigation.

The present study might have some limitations. First, the cross-sectional design implies that the associations that were found in our study may not represent true predictors of accelerated lung function decline. However, by relating duration of asthma to actual lung function, we calculated a "surrogate" decline in FEV_1/FVC for the groups as a whole (Fig 1). The regression lines clearly show a difference between non-atopic males and other subjects with adult-onset asthma, suggesting that gender and non-atopic status affect decline in lung function irrespective of asthma duration. Of course, prospective studies have to confirm our findings. Second, assessment of asthma duration was based on self report, and could therefore be influenced by recall bias. Despite careful attempts to avoid this, we cannot exclude this entirely. However, if airway disease was present during childhood, it was apparently not severe enough to be remembered, and therefore probably not severe enough to cause persistent airflow limitation during childhood. In addition, reported year of asthma onset appears to be rather accurate[30], and it is unlikely that any recall bias applies to non atopic male patients only.

The results of the present study have clinical and research implications. There is an increasing awareness of the heterogeneous character of asthma and its response to treatment. Our results show that amongst patients with asthma, the subgroup of male patients with non-atopic adult-onset asthma is more at risk of developing persistent airflow limitation than patients without these characteristics. These patients in particular require close monitoring of lung function and conscientious adjustment of asthma treatment, to prevent the development of persistent airflow limitation[31]. The challenging question remains whether clinical parameters and lung function measurements are adequate enough to monitor asthma and to prevent persistent airflow limitation, or that cellular[32] or molecular markers[33] of lower airway inflammation are necessary.

In conclusion, male gender and absence of atopy are independently associated with persistent airflow limitation in adult-onset asthma irrespective of age, smoking history or

body mass index. This implies that patients with newly diagnosed asthma, in particular males without known allergies should be monitored closely and treated carefully[31,34]. Future research should be directed towards a better understanding of the functional, cellular and molecular processes in the airways of these patients in order to detect potential causative factors and, eventually, to prevent excessive loss of lung function.

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Chapter 7

Anxiety, depression and personality traits in severe, prednisone dependent asthma

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INTRODUCTION

Mental disorders, including anxiety and depression are more prevalent in asthma as compared to the general population[1-8]. Although there is a clear relationship between anxiety, depression and asthma, the association with asthma severity is controversial. Some studies have shown significant differences in anxiety[9] and depression[10] in patients with severe asthma as compared to those with milder disease, while other studies did not find such differences[11-13].

Although these results are inconsistent, it has been clearly demonstrated that psychiatric morbidity in asthma is associated with reduced adherence to treatment[14], loss of asthma control[10;15], increased medical consumption[16] and increased exacerbations requiring bursts of oral corticosteroids[17;18]. Moreover, it has been shown that depression in chronic diseases such as asthma, has a greater effect on general health than depression or asthma alone[7].

Patients who use chronic oral corticosteroids are at higher risk of developing psychiatric comorbidities[19;20]. In patients with severe, prednisone-dependent asthma this may be bi-directional. On the one hand, the use of oral corticosteroids in severe asthma may lead to higher levels of anxiety and depression; while on the other hand, the underlying psychopathology may lead to less asthma control and thereby more prednisone dependence. Patients with steroid-dependent asthma seem therefore to be at highest risk of developing depression and anxiety disorders, and might benefit most from psychiatric interventions that contribute to asthma control.

In addition to anxiety and depression, specific personality traits have been associated with disease severity and poor outcome. Patients with near-fatal asthma have been shown to have less adaptive personality characteristics[15], and patients with severe asthma according to ATS criteria[21] appeared to have maladaptive coping styles[13] as compared to patients with milder disease. There are no reports comparing other personality traits between patients with mild-moderate and severe asthma.

Therefore, the aim of the present study was to investigate the prevalence of anxiety and depression symptoms in patients with severe, prednisone-dependent asthma and to investigate whether these patients have elevated dysfunctional personality traits as compared to patients with severe, non prednisone-dependent and mild-moderate disease. If so, this might have important implications for the management of patients with this disabling disease.

METHODS

Patients

Adult patients (18-80 yr) were recruited from the outpatient departments of 2 academic and 3 non-academic teaching hospitals in The Netherlands. Patients with mild-moderate asthma had to have a history of episodic dyspnea and wheezing, a documented reversibility in forced expiratory volume in 1 second (FEV_1) of > 12% predicted[22] or hyperresponsiveness to histamine (PC_{20} <8 mg/ml)[23]. Patient with severe asthma and prednisone-dependent and non-prednisone-dependent asthma had to meet the ATS criteria of severe asthma[21]. In addition, patients with prednisone dependent asthma were on maintenance therapy with prednisone (≥ 2.5 mg/day) for at least three months. Current smokers and patients with a smoking history of more than 15 pack years were excluded. The study was approved by the Leiden University Medical Centre Hospital Medical Ethics Committee and all patients gave written informed consent (P06.191).

Design

In this cross-sectional study all patients with asthma were asked to participate at their visit to the pulmonary outpatient clinics for a regular doctor's appointment.
In one visit, patients' characteristics were documented according to a structured questionnaire. Then the patients completed the 2 self-report questionnaires on psychological functioning. Finally, postbronchodilator FEV_1 was assessed using a handheld spirometer (Ferraris Respiratory Piko-1) according to ERS criteria[22].

Psychological questionnaires

The Hospital Anxiety and Depression Scale (HADS) is a widely used screening questionnaire to identify possible and probable cases[24] of depression (HADS-D) and anxiety (HADS-A)[25], which is reliable in patient and healthy populations[24]. The questionnaire contains 7 anxiety and 7 depression questions, each scoring 0-3 points. A cut off score of ≥11 points was used to define a probable case of anxiety or depression[26].
The NEO-Five-Factor Inventory (NEO-FFI) contains 60 multiple choice questions with a score ranging 1-5 for each answer. The questionnaire measures the 5 leading dimensions of the Big Five-model[27], neuroticism (emotional stability vs. lability), openness (susceptibility to new experiences), extraversion (out- or inwards directed energy and orientation), agreeableness (orientation towards others) and conscientiousness (conscience towards own behavior). In the present study the authorized Dutch translations were used for all questionnaires.

Statistical analysis

Demographic and psychopathological differences between patients with severe, prednisone-dependent asthma, non prednisone-dependent asthma and mild-moderate asthma were analyzed using one-way anova, chi-square tests and kruskall wallis tests. The sum scores obtained on the anxiety (HADS-A), depression (HADS-D), neuroticism, openness, extraversion, agreeableness and conscientiousness subscales (NEO-FFI) were analyzed as continuous variables.

Potential factors associated with anxiety and depression were analyzed as dichotomous independent variables, using the following contrasts: HADS-D ≥11 vs <11, HADS-A ≥ 11 vs. < 11, asthma duration ≥ 15 yr vs. < 15 yr (median) and BMI ≥ 28 vs. < 28 (median), age >49 vs <49 (median). Odds ratios for anxiety and depression as reference group were obtained by logistic regression analyses.

Asthma duration was defined as the number of years since asthma diagnosis. Number of smoking packyears was calculated by defining 1 packyear of smoking 20 cigarettes /day for a whole year. Chronic use of oral corticosteroids was defined as the daily use of prednisone for at least 1 month before entering the study. Analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). P-values less than 0.05 were considered significant.

Power

As a clinical meaningful difference on the HADS scale we defined a 2 unit difference. Because the HADS has a standard deviation of 4[25], we needed to include 128 patients in total to achieve 80% power for this medium effect size (significance level 0.05). As a clinical meaningful difference on the NEO-FFI scale we defined a 3 unit difference. Because the NEO-FFI has a standard deviation of 6[27], we needed to include 128 patients in total to achieve 80% power for this medium effect size (significance level 0.05).

RESULTS

Patient characteristics

One-hundred-eighty-seven patients, 67 patients with severe, prednisone-dependent asthma (20-77 yr), 47 with severe non-prednisone dependent asthma (19-70 yr) and 73 patients with mild-moderate asthma (18-75 yr) participated in the study. There was no significant difference between the prednisone-dependent patients and the group of severe, non prednisone dependent patients and mild-moderate asthma patients with respect to gender,

BMI and atopy (Table 1). However, prednisone-dependent asthma patients were older, had longer asthma duration and showed more severe airflow limitation as compared to the other patients.

Table 1. Baseline characteristics of patients with severe prednisone-dependent asthma vs. moderate-severe and mild-moderate asthma

	Prednisone-dependent n=67	Severe non-prednisone dependent n=47	Mild-moderate n=73	p-value
Age (yr)*	49.6 (12.9)	40 (16.5)	46.6 (15)	0.003
Female gender %	58.2	53.2	60.3	0.7
Asthma duration (yr)†	21 (9-36)	16 (5-21.8)	10 (2-27)	0.005
BMI*	28.2 (5.6)	26.5 (5.4)	26.1 (4.8)	0.07
Ex-smoker %	43.3	17	37	0.01
Packyears†	0 (0-4.1)	0 (0-0)	0 (0-3.3)	0.013
Atopy %	54.5	66.7	60.7	0.4
OCS dose (mg/day)†	10 (5-15)	0 (0-0)	0 (0-0)	<0.001
Duration of daily OCS (mth)	44 (3-360)	0 (0-0)	0 (0-0)	<0.001
ICS dose (µg/day)†	1000 (625-1250)	750 (500-1500)	250 (250-500)	<0.001
LABA %	100	91.5	68.5	<0.001
pbFEV1	81.0 (23.5)	96 (23.6)	102.4 (14.3)	<0.001

* mean (SD) † median (range)
BMI, body mass index; OCS, oral corticosteroids; ICS, Inhaled corticosteroids fluticason equivalent; LABA; long acting Beta agonist, pbFEV$_1$, forced expiratory volume in 1second post bronchodilator.

Psychological characteristics in prednisone-dependent vs severe non-prednisone dependent and mild-moderate asthma

Patients with severe prednisone-dependent asthma had significant higher scores on depression symptoms (HADS-D mean (SD) 4.5 (3.6) vs. 2.4 (2.4) and 3.4 (2.5), p = 0.002) and showed a trend towards higher anxiety symptoms (HADS-A 6.2 (4.4) vs. 4.8 (3.6) and 5.0 (2.9), p = 0.06) as compared to patients with severe or milder disease resp. (table 2).
The prevalence of clinically significant depressive symptoms (HADS-D score ≥11) and anxiety symptoms (HADS-A score ≥11) was higher in patients with severe, prednisone dependent asthma than in patients with severe non-prednisone-dependent or mild-moderate asthma (9% vs. 0% and 0%; p = 0.004) and (19% vs. 6.4% and 5.5%; p=0.01), respectively (Fig 1). There were no differences in personality traits between the three groups (Table 2).
Logistic regression analyses showed that patients with prednisone-dependent asthma were respectively 3.4 (95%CI: 1.0-10.8 p = 0.04) and 3.5 (95%CI: 1.3-9.6 p = 0.01) times more likely to have clinically significant symptoms of depression as compared to non prednisone-

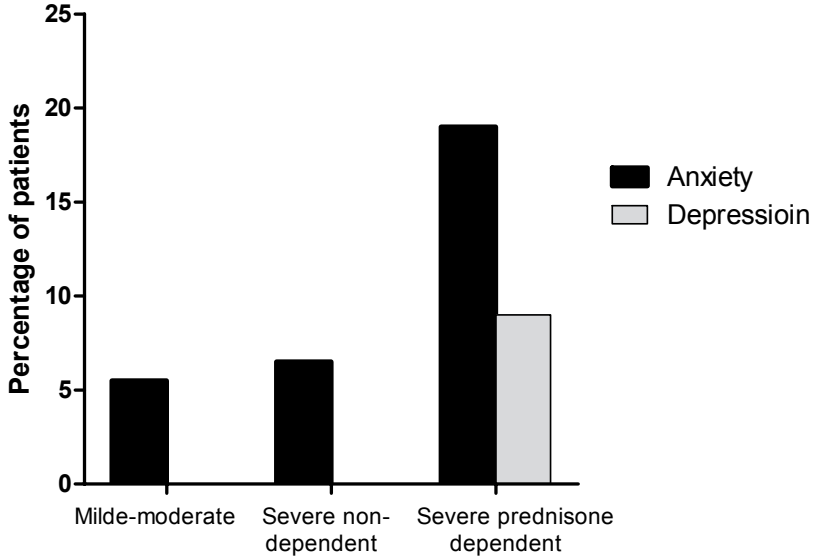
dependent severe asthma and mild-moderate asthma. In addition, as compared to mild-moderate asthma, patients with prednisone-dependent asthma were 2.5 (95%CI: 01.1-5.5, p = 0.02) times more likely to have significant symptoms of anxiety and 1.6 (95%CI: 0.7-3.7, p = 0.2) times more likely as compared to non-prednisone dependent severe asthma, although the latter one was not significant. In addition, there were no associations found between depression or anxiety and age, asthma duration, BMI, smoking history and dose of OCS. Also, there was no association found between the dose of prednisone and anxiety or depression.

Table 2. Psychological Questionnaire scores for patients with severe prednisone-dependent, moderate-severe and mild-moderate asthma

		Prednisone-dependent n=67	Severe non-prednisone dependent n=47	Mild-moderate n=73	P-value
HADS	Anxiety	6.2 (4.4)	4.8 (3.6)	5.0 (2.9)	0.07
	Depression	4.5 (3.6)	2.5 (2.4)	3.4 (2.5)	0.002
NEO-FFI	Neuroticism	33.7 (5.6)	32.2 (3.9)	31.8 (2.8)	0.07
	Extraversion	38.6 (4.7)	39 (4.1)	39 (3.6)	0.8
	Openness	37.4 (4.2)	36.4 (4.2)	37.4 (3.3)	0.3
	Agreeableness	35 (4.3)	36 (5.2)	35.8 (4.5)	0.4
	Conscientiousness	40.2 (4.3)	39.9 (4.1)	40.8 (3.1)	0.4

Values expressed in mean (SD). HADS, Hospital Anxiety and Depression Scale; NEO-FFI, Neo-Five-Factor Inventory.

Figure 1. Percentage of patients with high anxiety and depression symptoms in severe prednisone-dependent asthma as compared to patients with severe non-prednisone dependent asthma and mild asthma.



DISCUSSION

In the present study we found a higher prevalence of psychological distress (depression and anxiety) in patients with severe, prednisone-dependent asthma as compared to patients with severe, non-prednisone dependent or mild-moderate disease. Patients with prednisone-dependent asthma were 3.5 times more likely to have clinically significant depression symptoms, and about 2.5 times more likely to have significant anxiety symptoms as compared to patients with severe or mild-moderate disease. With respect to personality traits we found no differences in patients with severe, prednisone-dependent asthma and the other groups. This implies that this particular group of patients with prednisone-dependent asthma should be screened routinely for anxiety and depression symptoms and offered psychiatric care if needed.

The present study is the first, to our knowledge, to systematically investigate psychological distress and personality traits in patients with severe, prednisone-dependent asthma as compared to less severe, non-prednisone dependent asthma. Previous studies have investigated the prevalence of depression or anxiety symptoms (HADS score >11) in asthma irrespective of disease severity. They found prevalences ranging from 10-13.6 % and 9-31.6 % respectively[18;28;29].
The non-prednisone dependent asthma patients in our study had HADS-A and HADS-D scores similar to that of the general population [25;30]. However, patients with severe prednisone-dependent asthma had higher scores, similar to those of (non-psychiatric) medical outpatients[25]. This indicates that the prevalence of anxiety and depression symptoms in severe prednisone-dependent asthma is high, but not higher than in other outpatients. The prevalence of anxiety and depression in severe non-prednisone dependent asthma and mild-moderate asthma is within the normal range.

Studies that compared the prevalence of anxiety and depression between patients with severe and milder forms of asthma found conflicting results. Several studies showed no differences between patients with severe and mild-moderate asthma[11-13], while other studies found higher levels of psychopathology in patients with more severe disease[31-33]. The present study sheds new light on these conflicting findings by showing that only prednisone-dependent severe asthma patients have more anxiety and depression, which suggests that these psychological conditions are associated with prednisone treatment rather than with disease severity per se.

With respect to personality traits, relatively few studies have been performed in severe asthma. Several studies found that patients with severe asthma[13] and near-fatal asthma[15] show less

adaptive personality characteristics as compared to those with milder disease, although this relationship was not always found[12]. In these studies different methods were used to measure personality traits, and therefore the results are difficult to interpret. One study investigated the "Big 5" personality profile in a Portuguese asthma population[34]. Neuroticism scores were positively associated with asthma severity, which is consistent with the trend we found in our study. They also found extraversion and openness scores to be lower with increasing asthma severity, which we did not find. Interestingly, all patients with asthma in our study had relatively low scores on conscientiousness and very low scores on agreeableness as compared to the general population[35], for which we have no explanation. Obviously, more studies are needed to further investigate the relationship between personality traits and asthma severity.

The causality of the association between prednisone dependent asthma and anxiety and depression, might be bidirectional. The most likely explanation is that depression and possibly anxiety are a direct effect of corticosteroid treatment. One study found an association between the use of inhaled corticosteroids and depressive symptoms[36] and it has been shown that patients taking (long term) prednisone therapy tend to show higher scores on psychiatric symptoms[19;37;38]. This result is consistent with the observation of an increased prevalence of psychopathology in patients with long-term cured Cushing's disease, suggesting irreversible effects of previous glucocorticoid excess on the central nervous system[39].
Alternatively, psychological stress might be the cause of prednisone-dependency in patients with asthma. Psychological distress has been shown to be associated with more severe asthma symptoms[40], increased health care utilization[16], and frequent exacerbations[17] requiring oral corticosteroid bursts. It could be speculated that psychological stress leads to increased perception of asthma symptoms or even more severe airway inflammation[41], which may the cause of failure to control asthma with inhaled medications alone or to discontinue oral corticosteroids after an acute exacerbation.
Finally, psychosocial stress could be the consequence of chronic severe asthma itself. The experience of frequent asthma attacks and/or chronic impairment in social functioning might obviously result in anxiety and depression[42]. However, our results show an association with prednisone dependent asthma and not with severe non-prednisone dependent asthma. Therefore, this explanation is the least likely.

Although this study was performed in a well-defined group of patients and was adequately powered, it might have some limitations. The design of the present study is cross-sectional; therefore we cannot be certain that the results are consistent over time. Asthma as well as anxiety and depression are conditions with variable degrees of symptoms, and consistency over time in these patients has never been investigated. Nevertheless, the HADS has been

well validated in the general population, in general practice and in psychiatric patients[26]. In addition, the HADS has proven to be adequate for repeated assessment of probable anxiety and depression at subsequent visits for follow-up[26].
Second, patients had to use prednisone on a daily basis for at least one month. It could be speculated that, if anxiety and depression are adverse effects of oral corticosteroids, this period may be too short. However, at least one study showed that anxiety and depression can develop within 5 days after starting oral corticosteroids[19]. In addition, the vast majority of our patients used chronic oral prednisone for many years. Therefore, we do not think this influenced the results of the present study.

The results of the present study have clinical and research implications. Physicians should be aware that oral corticosteroids may induce psychiatric adverse effects, such as anxiety and depression which may in turn influence asthma severity and control. Therefore, it might be worth to screen patients with severe prednisone-dependent asthma for anxiety and depression symptoms. In short-term intervention studies promising effects of pharmaceutical or psychosocial interventions have been observed[43;44], but more prospective studies are needed in this category of patients to see if better asthma control or less oral corticosteroid-dependency can be obtained on the long term.

In conclusion, we found significantly more anxiety and depression symptoms in patients with severe prednisone-dependent asthma as compared to patients with non-steroid dependent severe asthma or mild-moderate asthma. Patients with prednisone dependent asthma are 3.5 times more likely to have significant symptoms of depression and 2 times more likely to have significant symptoms of anxiety than their non-steroid dependent counterparts. Therefore, these patients deserve to be screened for depression and anxiety, and offered psychiatric or psychosocial care if needed. Hopefully, such interventions will lead to better control of the disease and less need for oral corticosteroids.

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Chapter 8

Predictors of poor adherence to inhaled corticosteroid therapy in patients with asthma, COPD and other chronic respiratory diseases.

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(Submitted)

INTRODUCTION

It is now generally accepted that one of the major contributions to treatment failure in many chronic conditions is non-adherence[1]. In asthma, adherence rates have been estimated between 30-70%[2-5] and in COPD these numbers are similarly low, being 31-54%[6, 7]. Non-adherence has been associated with poor asthma outcomes, hospital admissions, emergency department visits and oral corticosteroid bursts[8, 9]. In COPD non adherence has been associated with worse clinical outcomes, decreased quality of life and less work productivity. Poor adherence to inhaled corticosteroid therapy is highly prevalent in patients with difficult-to-control asthma and that is why the Innovative Medicine Initiative (IMI) has recently recommended in an international consensus statement that these patients should be routinely checked for adherence before being diagnosed with severe, refractory asthma[10]. The differentiation between patients with uncontrolled disease and truly severe disease is critical indeed, because only for the latter novel targeted therapy might be indicated.

Investigating adherence is challenging and most studies on non-adherence in asthma have been performed in cohorts of patients with mild-moderate asthma or in cohorts with low patient numbers. Because of this, adherence rates in patients with the highest burden of illness or most difficult to manage disease, remain scarce[11].

Previously, Gamble and colleagues showed that almost 80% of the patients with difficult-to-control asthma who were referred to a specialized asthma clinic in the UK were taking their inhaled corticosteroids not according to prescription[3]. These results need, however, to be validated in larger cohorts of patients with difficult-to-control asthma in primary and secondary care. In addition, it is important to identify factors that are associated with non-adherence to treatment in asthma and COPD, as well as in other respiratory diseases.

The primary aim of our study was to assess the prevalence of non-adherence to inhaled corticosteroids in a large cohort of primary and secondary care patients who had asthma and were prescribed high intensity asthma treatment (high dose ICS, or medium-high doses of ICS plus continuous low dose oral corticosteroids[10]). The second aim of our study was to compare adherence rates amongst asthma patients on high intensity treatment between those whose disease was controlled or uncontrolled, and between those with asthma, mixed asthma/COPD, COPD and other respiratory disorders. The third aim was to identify factors associated with non-adherence to inhaled corticosteroid treatment in these specific subgroups.

METHODS

Participants

Automated dispensing records from 47 community pharmacies in the Netherlands were used to identify all patients with at least one prescription for an inhaled corticosteroid in 2011.
In The Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling collection of complete medication histories of individual subjects over a long period of time.
From these patients, all patients aged >18 yr using high dose ICS (i.e. >1000 µg/day fluticason or equivalent) plus long acting beta-2-agonists (LABA) or medium high dose ICS (> 500ug/day fluticason or equivalent) plus daily oral corticosteroids (OCS) and LABA. Patients were excluded if they received only one prescription without a refill, to avoid inclusion of patients using ICS only for a selected period of time. All selected patients were asked to complete a questionnaire on diagnosis, demographics, smoking history and health care utilisation, as well as the Asthma Control Questionnaire (ACQ)[12].

Ethics and confidentiality

This study was approved by the Medical Ethics Committee of the Academic Medical Centre (METC number: 2011_255; NTR/TC number 3546). All patient data were coded. Individual pharmacists kept the code to identify individual patients. A intermediate party (the supplier of the pharmacy information system) kept the key to identify the participating pharmacists.

Measuring adherence

All dosages of inhaled corticosteroids were converted to fluticasone equivalent according to the WHO DDD-index 201213. Adherence was expressed as a proportion calculated by dividing the number of dispensed dosages in 2011 by 365 x the prescribed daily dose (e.g. patient is prescribed 2 daily dosages of an ICS and has been dispensed 600 dosages; adherence will be (600/(2X365))x100%=82%). Adherence was defined as very poor (adherence <50%), poor (adherence 50-80%), adherent (adherence 80-100%) or overuse (>100%).

Variables

"Difficult-to-treat asthma" was defined as uncontrolled asthma despite the prescription of ≥ 1000 µg/day fluticasone equivalent, or ≥ 500µg/day fluticasone equivalent + a maintenance dose of ≥5 mg prednisone per day for at least 30 days. Uncontrolled asthma was defined

by an ACQ score >1.5 or ≥2 severe exacerbations in the previous year or ≥1 hospitalization, ICU stay or mechanical ventilation in the previous year[10]. Four categories of patients with respiratory diseases were distinguished from the questionnaires: "Asthma" was defined by a self-reported diagnosis of "asthma", "COPD" or "chronic bronchitis" combined with a smoking history < 10 packyears. "Mixed asthma/COPD" was defined as self-reported "asthma", "COPD" or "chronic bronchitis" combined with a history of childhood respiratory symptoms, atopic disease or nasal polyposis combined with a smoking history of >10 packyears. "COPD" was defined as self-reported "asthma", "COPD" or "chronic bronchitis" combined with a smoking history of >10 packyears, but no history of childhood respiratory symptoms, atopy or nasal polyposis. "Other respiratory diseases" were defined as self-reported other diseases than asthma, COPD or chronic bronchitis, such as sarcoidosis, alpha-1-anti-trypsin deficiency and pigeon breeders' disease. One smoking packyear was calculated as smoking 20 cigarettes a day for a whole year. The number of asthma or COPD exacerbations was defined as the self-reported number of prednisone bursts needed to control increased respiratory symptoms in 2011.

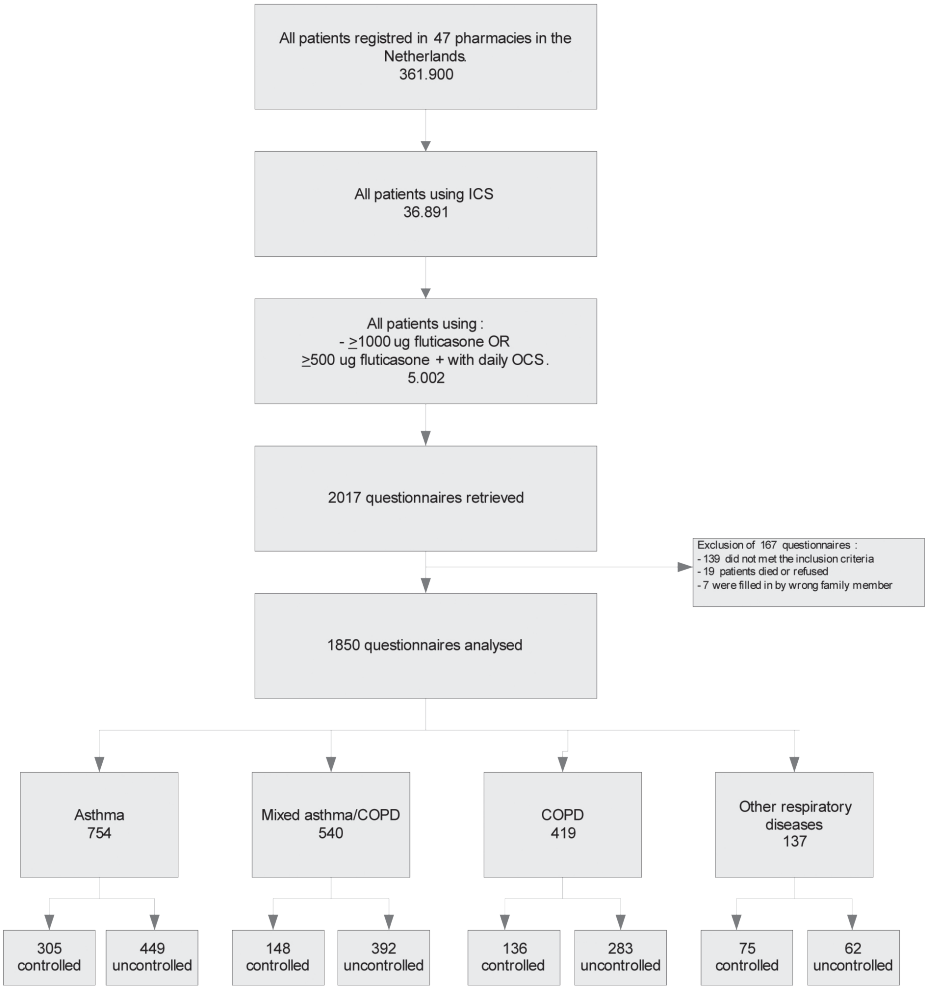
Statistical analyses

For comparison between groups X_2-tests were used for proportions, unpaired t-tests for parametric variables and Kruskall Wallis for nonparametric variables. Factors associated with adherence were assessed by univariate and multivariate logistic regression analyses. All analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL). P-values <0.05 were considered statistically significant.

RESULTS

Approximately 361.900 patients were registered in the 47 community pharmacies of which about 36.891 (10.1 %) received at least one prescription for an ICS. Of these patients, 5002 used high dose ICS or medium-high dose ICS plus continuous oral corticosteroids. To these patients questionnaires were sent of which 2104 were retrieved. Eighty-seven questionnaires were lacking identification codes and could therefore not be retraced to the correct patient, and 167 patients were excluded because of various reasons (Figure 1). Therefore, the questionnaires of 1850 participants were used for the analyses.

Figure 1. Flow chart



Patient characteristics

Based on the questionnaires seven hundred fifty-four (40.8%) patients were diagnosed with asthma, of which 305 (16.5%) had controlled asthma (ACQ ≤1.5 or <2 exacerbations in the past year), and 449 (24.3%) patients had uncontrolled asthma (ACQ ≥1.5 or ≥2 exacerbations in the past year). Five hundred forty (29.2%) patients had mixed asthma/COPD, (148 (8%) controlled and 394 (21.2%) uncontrolled disease). Four hundred nineteen patients (22.6%) had COPD and 138 (7.4%) had other respiratory diseases (figure 1). Characteristics of patients with "asthma""mixed asthma/COPD", COPD and other respiratory diseases are summarized in

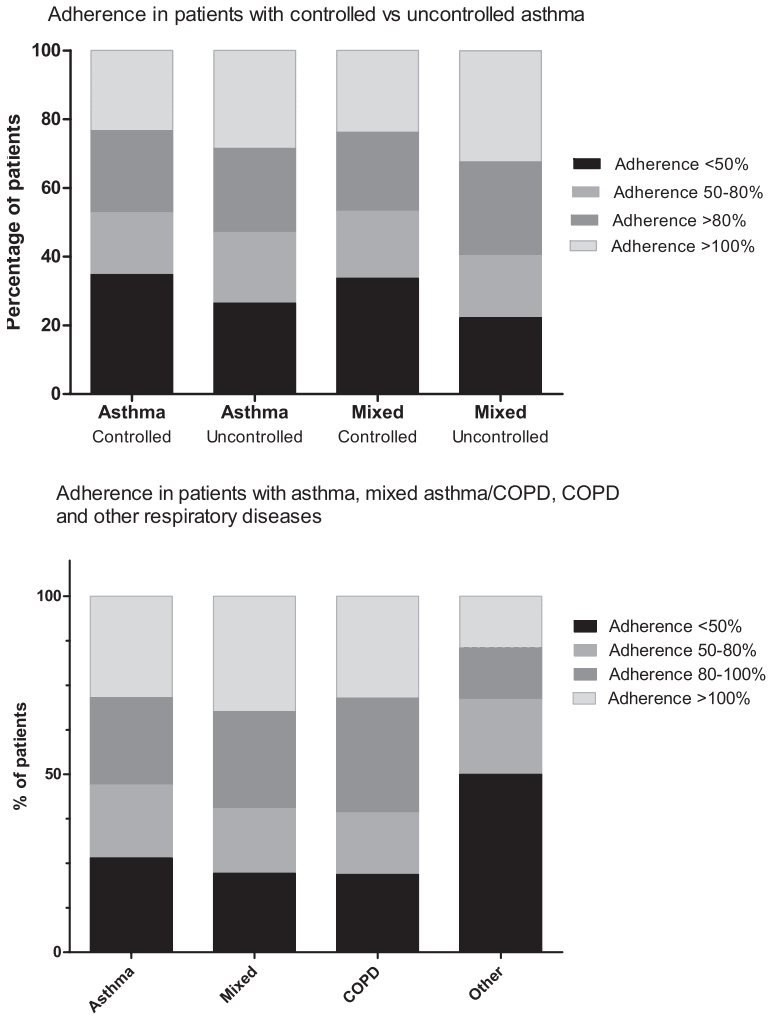
Table 1. The mean age of the patients was 64 years and was higher in patients with "COPD" as compared to "asthma" or "mixed asthma/COPD). The majority of patients were female (56%) with the highest percentage of females in the group of patients with asthma (63%). Of all patients 55% were treated in secondary care, varying between 50% and 60% amongst the subgroups. Ninety-four percent of the patients were atopic and 17% had (a history of) nasal polyposis. With respect to health care utilisation, patients with "asthma" or "mixed asthma/COPD" had more hospitalisations and exacerbations as compared to those with COPD or other respiratory diseases.

Table 1. Characteristics of patients asthma, mixed asthma, COPD or other respiratory diseases.

	All patients	Asthma	Mixed asthma	COPD	Other	p-value
Age*	63.9 (14.6)	60.5 (16.8)	64.2 (12.2)	69.1 (10.9)	65.1 (14.5)	<0.01
Gender (female)%	55.7	63.2	48.5	51.2	47.1	<0.01
BMI*	27 (5.9)	27.1 (5.9)	27.3 (6.1)	26.1 (5.9)	27.3 (5.3)	0.01
Age of medication*	44.5 (21.5)	36.1 (22.2)	44.1 (19.9)	57.7 (13.8)	49.9 (20.5)	<0.01
Childhood symptoms %	35.1	45.2	53.8	0	18.5	<0.01
Secondary care %	55	51.7	56.3	60.0	50	0.01
Hospitalistations%						0.14
- 0	82.8	85	81.7	79.7	83.9	
- 1-2	13.7	11.6	14	7	14.6	
- 3+	3.5	3.5	4.3	1.3	1.5	
Exacerabations%						<0.01
- 0	47.2	49.3	41.7	46.9	60.6	
- 1-2	37	34.7	38.9	39.1	32.8	
- 3+	15.8	15.7	19.4	14	6.6	
Atopy %	49.5	65.7	66.2	0	40.8	<0.01
Non-atopic symptoms%	67.6	76.1	74.2	51.9	41.9	<0.01
Nasal polyposis %	17.4	22.1	23.6	0	20.8	<0.01
Smoking %						<0.01
- Never	32.7	72.9	0	0	38.3	
- Active	19.4	5	33.9	27.5	18	
- Ex-smoker	47.8	22	66.1	72.5	43.8	
Packyears†	13 (0-32.5)	0 (0-0)	0 (0-9)	35 (22.5-48)	8.4 (0-23.8)	<0.01
ICS dose# prescribed†	1000 (6000-1000)	1000 (600-1000)	1000 (600-1000)	1000 (600-1000)	1000 (600-1000)	0.76
LABA dose prescribed†	24 (19.5-24)	24 (19-24)	24 (19-24)	24 (20-24)	24 (19-24)	0.74
OCS %	56.5	53.2	60	58.9	50.4	0.01
ACQ*	1.3 (0.6-2.3)	1,2 (0.6-2.2)	1.8 (1.0-2.5)	1.5 (0.8-2.1)	1.1 (0.3-1.7)	<0.01

* Mean (SD) † Median (1th and 3th interquartile) #Fluticasone equivalents

Figure 2 en 3



Adherence in patients with asthma and mixed asthma/COPD

Of the patients with uncontrolled asthma 26.5% were very poorly adherent, 20.5% were poorly adherent, 24.5% were adherent and 28.5% were overusing their inhaled corticosteroid medication. This was worse than in patients with uncontrolled mixed asthma/COPD in which adherence rates were 22.2%, 18.1%, 27.3% and 32.4% resp ($p = 0.02$). As compared to controlled disease, patients with uncontrolled asthma or mixed asthma/COPD were more often overusing their inhaled glucocorticoids (ICS) (21.2% vs. 29.1%, $p=<0.01$) and were less often very poorly adherent (35.5% vs. 21.4% resp. $p <0.01$) (Table 1, Figure 2).

Comparison of adherence rates between (mixed) asthma, COPD and other respiratory diseases

Patients with asthma were less adherent to ICS therapy than patients with mixed asthma/COPD or COPD, but patients with other respiratory diseases were the least adherent to ICS therapy (very poorly adherent 29.8%; 25.4%; 25.1% and 49.6% resp). Patients with COPD were the ones that most often used their medication according to prescription (31%) and patients with mixed asthma/COPD were the ones that most often overused their medication (30%) (Table 2, Figure 3).

Factors associated with very poor adherence to inhaled corticosteroids

In the whole group of patients with asthma and mixed asthma/COPD, univariate logistic regression analysis showed that younger age (B = 0.013, p = 0.002, OR 1.02), treatment in primary care (B = 0.69, p = <0.001, OR 2.01), current smoking (B = 0.48, p-value <0.001, OR 1.61), no use of prednisone ((B = 0.39, p = 0.002, OR 1.47) and having controlled disease (B = 0.48, p = <0.001, OR 1.61) were associated with very poor adherence (<50%) to ICS treatment. Multivariate logistic regression analysis showed that only younger age (B = 0.009, p = 0.04, OR 1.02), treatment in primary care (B = 0.6, p = <0.001, OR 1.82) and having controlled disease (B = 0.43, p = 0.05, OR 1.53) were independently associated with very poor adherence to ICS treatment. These analysis were also performed separately for patients classified as having asthma or mixed asthma/COPD: For patients with asthma univariate logistic regression analysis showed that younger age (B = 0.01, p=0.01, OR = 1.1), treatment in primary care (B = 0.76, p = <0.001, OR 1.14), no use of daily oral corticosteroids (B = 0.37, p = 0.02, OR 1.45) and having controlled disease (B = 0.39, p = 0.01, OR 1.47) were associated with very poor adherence. Multivariate logistic regression analysis showed that only treatment in primary care (B = 0.67, p = <0.001, OR 1.6) was independently associated with very poor adherence to ICS.

For patients with mixed asthma/COPD univariate logistic regression analysis showed associations between very poor adherence and younger age (B = 0.02, p = 0.04, OR 1.02), treatment by a general practitioner (B = 0.58, p = 0.004, OR 1.79) current smoking (B = 0.67, p = 0.001, OR 1.96) and having controlled disease (B = 058, p = 0.006, OR 1.78). Multivariate regression analysis showed that only current smoking was independently associated with very poor adherence in patients with mixed asthma/COPD (B = 0.51, p = 0.02, OR 1.6).

Table 2. Characteristics of patients controlled and uncontrolles asthma and mixed asthma.

	Asthma		Mixed asthma/COPD		p-value
	Controlled	**Uncontrolled**	**Controlled**	**uncontrolled**	
Age*	59.2 (17.7)	61.3 (16.6)	63.6 (12.8)	64.4 (12)	<0.001
Gender (female)%	59.3	66.4	43.3	50.5	<0.001
BMI*	26.4 (4.8)	27.6 (6.5)	27.1 (5.2)	27.4 (6.3)	0.07
Age of medication*	36.5 (22)	35.9 (22.3)	46.3 (20.6)	43.4 (19.6)	<0.001
Childhood symptoms %	43.1	47.3	53.5	53.9	0.02
Secondary care %	38.2	60.9	36.4	63.7	<0.001
Hospitalistations%					<0.001
- 0	93.4	79.2	95.2	76.7	
- 1-2	6.6	15.4	4.8	17.4	
- 3+	0	5.4	0	5.9	
Exacerabations%					<0.001
- 0	89.5	22	92.6	22.4	
- 1-2	10.5	51.2	7.4	50.8	
- 3+	0	26.7	0	26.8	
Atopy %	66.1	65.4	63.2	67.4	0.8
Non-atopic symptoms%	66.7	82.4	54.5	81.7	<0.001
Nasal polyposis %	19.4	24	26.2	22.6	0.4
Smoking %					<0.001
- Never	73.4	72.6	0	0	
- Active	6.2	4.2	38.4	32.2	
- Ex-smoker	20.3	23.2	61.6	67.8	
Packyears†	0 (0-0.8)	0 (0-1.2)	27 (19-42)	28 (18-43)	<0.001
ICS dose# prescribed†	1000 (850-1000)	1000 (600-1000)	1000 (1000-1000)	1000 (600-1000)	<0.001
LABA dose prescribed†	24 (20-24)	24 (19-24)	24 (21.3-24)	24 (18.8-24)	0.4
OCS %	24.2	76.2	26.4	76.8	<0.001
ACQ*	0.72 (0.46)	1.92 (1.04)	0.83 (0.45)	2.17 (1.02)	<0.001

* Mean (SD) † Median (1th and 3th interquartile) #Fluticasone equivalents

Table 3. Adherence rates in(mixed) asthma, COPD and other respiratory diseases

	Asthma	Mixed asthma/COPD	COPD	other	p-value
Adherence					<0.001
- <50	29.8	25.4	25.1	49.6	
- 50-80	19.5	18.5	17.9	18.2	
- 80-100	24.3	26.1	31	20.4	
- >100	26.4	30	26	11.7	

DISCUSSION

The results of the present study show that in a large cohort of primary and secondary care patients the majority of patients with asthma were non-adherent to ICS treatment. Remarkably, adherence rates were lower in patients with controlled asthma as compared to those with uncontrolled disease. Adherence rates were lower in asthma than in COPD, but higher than in other respiratory diseases. Amongst all patients with asthma younger age, treatment in primary care and having controlled disease were independently associated with very poor adherence. In "pure" asthma, the only independent factor associated with very poor adherence was being treated in primary care, whereas in mixed asthma/COPD current smoking was the only independently associated factor. These findings confirm that poor adherence is highly prevalent amongst asthma patients, and show that poor adherence is not confined to uncontrolled asthma, but occurs in controlled asthma as well.

Our study confirmed a high prevalence of non-adherence in all types of airway diseases, including asthma, mixed asthma/COPD, COPD and other airway diseases. These adherence rates are lower than suggested in a previous report of the WHO showing that adherence rates in chronic diseases is about 50%[1]. Our results are more in line with two studies in difficult-to-control adult asthma performed in patients referred to specialized asthma clinics, showing very poor adherence rates of 31-35%[3, 14]. Our results extend these data by showing similar low adherence rates in a very large population sample of difficult-to-control asthma patients, which included patients treated in primary care.
Our study is the first that compared patients with controlled and uncontrolled asthma, to our surprise, patients with controlled asthma had even lower adherence rates as compared to those with uncontrolled disease. It seems likely that these patients may be less adherent because their asthma is already well-controlled with irregular use of inhaled corticosteroids. Such "non-adherence" can be considered as appropriate self-management. Although it would probably be more appropriate to switch patients who have been on high dose inhaled steroids to a regular lower dose instead of using a higher dose irregularly.

Remarkably, when comparing different subgroups of patients treated with high dose ICS, those with COPD were the most adherent to ICS therapy, whereas those with respiratory diseases other than asthma or COPD tended to be the least adherent to ICS therapy. This suggests, that non-adherence to ICS is not related to the medication per se, but also varies between diseases, being lower in COPD than in asthma. One explanation for this might be that adherence is symptom related, since COPD patients often have more constant daily symptoms, while in asthma symptoms are more often intermittent. However, a study by Mann and colleagues showed that adherence in patients with asthma was not modulated by

patient reported symptoms[15]. Therefore, more research is needed to explain these differences in adherence rates between diseases.

The most striking factor associated with poor asthma control was being treated in primary care as compared to secondary care. Previous research into factors associated with non-adherence to controller therapies in asthma showed that many factors can be detected, ranging from African-American race[4, 16], female gender[4], younger age[4], certain personality tariats[17], socioeconomic factors[18], severity of disease[18] and poor asthma control[4, 19]. Our study extends this list showing that treatment by the general practitioner, and having controlled disease were also associated with very poor adherence. In addition, current smoking was associated with very poor adherence in patients with mixed asthma/COPD. One could speculate that patients in primary care are less intensively monitored and therefore more often non-adherent to their ICS treatment. However it is more likely that patients in primary care may have milder disease that can be well controlled on lower ICS doses than originally prescribed. In any case, there is an important role for the primary care providers to discuss adherence with their patients. As mentioned earlier it is recommended to taper the dose in case patients are well controlled on high doses instead of irregular use by the patient without consulting the physician.

There are many reasons why a patient could be non-adherent to therapy. A previous study investigating adherence in 230 patients using inhaled corticosteroids showed that in 45% of the cases the main reason for discontinuation ICS was the lack of symptoms. Remarkably, a substantial proportion of these patients still reported residual clinically significant symptoms. In addition, 27.3% could not give clear reason for discontinuation[20]. Another study investigating medication beliefs in patients using ICS showed that almost half of the patients had doubts about the need for a preventer inhaler, and 42% had concerns about potential side effects. This suggests that patients balance the necessity for inhaled corticosteroids against their concerns about the side effects[21].

For the clinician, the present study shows that very poor adherence should be one of the most important factors to consider in patients with difficult-to-treat asthma. Non-adherence should always be addressed and discussed, even if asthma is controlled, as it may be related to numerous clinical and personal characteristics. Non-adherence should also be checked before considering treatment with targeted biologicals. By discussing non-adherence and sharing treatment decisions with the patients, one could improve adherence and hopefully asthma outcome[22].

The strength of the present study lies in the large number of participants with difficult-to-control respiratory disease, representing a large population in the Netherlands. In addition, the population encompassed all patients using high dose inhaled corticosteroids, including those treated by the general practitioner.
Our study may also have some limitations. First, with prescription fillings one may confirm non-adherence but patients who fill their prescriptions are not necessarily taking their medication. Therefore, adherence rates in the present studies might have been overestimated, although our results in asthma are similar to those reported in previous studies. Second, patients who are non-adherent are less likely to participate in studies and return questionnaires, which might have been another reason for overestimating the percentage of adherent patients. Third, as part of a personalized management strategy some patients might have reduced their ICS use as soon as their disease was controlled. This therapeutic strategy could have lead to an overestimation of the percentage of non-adherent patients in those with controlled disease.

In conclusion, non-adherence is a major problem in the treatment and management of difficult-to-treat airway diseases as it has been shown that the majority of patients are not taking their inhaled corticosteroids adequately, irrespective of asthma control. Therefore, clinicians should be aware that the majority of their patients are non-adherent and medication prescription refills should be checked when a patient has loss of control or before considering intensifying or adapting treatment.

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Chapter 9

Summary and General Discussion

SUMMARY – INSIGHTS INTO DISEASE SEVERITY IN ADULT ASTHMA

Background of the thesis

The development and expression of asthma subphenotypes are influenced by many factors and thereby complicates effective clinical care. The classical, most prevalent phenotype of asthma is associated with atopy, starts in early childhood, and typically runs in families[1]. However, there is an increasing understanding that there are other underdiagnosed and unrecognized phenotype of asthma that starts in adulthood[2-4]. As compared to childhood onset asthma, these phenotypes appear to be more severe, more likely to persist and show a faster decline in lung function[5;6]. However, to better understand mechanisms of (severe) adult-onset asthma and to identify relevant clinically well recognized subphenotypes of adult-onset asthma, further research in this phenotype is needed. Therefore, the first part of this thesis focusses on defining clinical phenotypes of adult-onset asthma by cluster analyses, and finding factors associated with more severe disease and with disease outcome. To that end, a cohort of 200 patients with adult-onset asthma was characterized by clinical, functional and inflammatory markers and cross-sectionally evaluated.
In the second part of this thesis we focussed on factors influencing asthma and disease outcome in terms of co-morbidity (anxiety and depression) and adherence to medication regimens. The main results, conclusions and implications of these studies are summarized below.

Conclusions of the studies

Adult-onset asthma: subphenotyping and identifying severe disease

In chapter 2 a review was written about phenotypes of adult-onset asthma and possible targeted therapies. The aim of this review was to provide an overview of the incidence and prevalence of adult-onset asthma, to provide an overview of studies in adult-onset asthma and describe clinically recognized subphenotypes of this disease. Based on this review we can conclude that, the incidence of adult-onset asthma is estimated to be about 4.6/1000 per year for women and 3.6/1000 per year for men with a trend towards higher estimates of adult incidence in later studies. The prevalence of adult-onset asthma is unknown, although amongst patients with severe asthma this is estimated to be as high as 50%, much higher than in the general asthma population. Also, in adult-onset asthma a variety of etiologic factors have been implicated as risk factors for asthma onset, such as occupational exposures, female sex hormones, smoking, obesity and viral infections. Previously several cluster analyses in patients with (severe) asthma identified different subsets of adult-onset

disease. One non-atopic, inflammation predominant subset with fixed airflow limitation and one late onset obese female preponderant phenotype. In addition, there may be additional clinically recognized subphenotypes in adult-onset disease that are excluded from cluster analyses, such as asthma that develops in smokers. The general therapeutic approach of patient with adult-onset asthma is similar to that of childhood onset asthma, although this could be extended towards more personalized medicine as adult-onset asthma has specific, clinical subphenotypes with different symptoms, asthma course and co-morbidities.

In chapter 3, a population of 200 patients with adult-onset asthma was described and subphenotyped based on cluster analyses. This study showed that three clusters of patients with adult-onset of disease could be described based on distinct clinical and inflammatory features. The first cluster consisted of patients with severe eosinophilic inflammation-predominant asthma with persistent airflow limitation and few asthma symptoms. The second was characterized by obese females with frequent asthma symptoms and high health care utilisation, but normal lung function and low sputum eosinophils. The last cluster showed patients with mild to moderate, well controlled asthma with normal lung function and low inflammatory markers.
These results confirm and extend the phenotypic characteristics of previously proposed clusters of severe adult-onset asthma by showing their consistency in a different population of only adult-onset asthma with different treatment regimens. The identification and reinforcement of these three subphenotypes in a different cohort may raise novel hypotheses on different mechanisms of adult-onset asthma subphenotypes, asthma severity and may give clinicians stronger directions for more personalized management strategies.

In Chapter 4 we compared 78 patients with severe adult-onset asthma to 98 patients with milder disease. Patients with severe disease showed nasal symptoms and nasal polyposis, increased exhaled nitric oxide levels, higher blood neutrophils and sputum eosinophilia despite treatment. This suggests that severe adult-onset asthma represents a specific phenotype with different underlying pathophysiology as compared to milder disease, but also as compared to severe asthma in general.

In chapter 5 we assessed the frequency of CRS in the early stages of adult-onset asthma (<1 year diagnosis) and investigated whether CRS is associated with eosinophillic airway inflammation in the lower airways. The results of this study showed that 54% of the patients had chronic rhinosinusitis at time of asthma diagnosis, of which 20% included nasal polyposis. Patients with nasal polyposis had the highest amount of sputum eosinophils and exhaled nitric oxide levels. Moreover, the extend of CT-sinus deviations (scored according to Lund & McKay) were independently associated with sputum eosinophil percentages and exhaled

nitric oxide levels. Based on these results we concluded that in patients with newly diagnosed asthma is highly prevalent and might be an early sign of the severe eosinophilic phenotype.

In Chapter 6 we investigated factors associated with lung function decline in adult-onset asthma. This was based on a hypothesis that was generated by a previous study showing that patients with difficult-to-treat adult-onset asthma show a faster decline in lung function as compared to difficult-to-treat childhood onset asthma. In this study we showed that male gender and absence of atopy are independently associated with persistent airflow limitation in adult-onset asthma irrespective of age, smoking history or body mass index.

Evaluating severe asthma.

In the second part of this theses we investigated a few specific aggravating factors that might influence asthma severity and control. It has been shown that anxiety and depression are highly prevalent in asthma, but a clear relationship with disease severity is lacking. Therefore we investigated anxiety, depression and personality traits in patients with mild, severe and severe prednisone-dependent asthma (chapter 7). When comparing these groups of patients we found significantly more anxiety and depression symptoms in patients with severe prednisone-dependent asthma as compared to patients with non-steroid dependent severe asthma or mild-moderate asthma but no differences in personality traits. This suggests that not asthma severity but treatment with is associated with oral corticosteroids is associated with psychiatric adverse effects, including anxiety and depression, which may in turn influence asthma severity and control. Therefore, it might be worth to screen patients with severe prednisone-dependent asthma for anxiety and depression symptoms.

In the last study of this thesis (chapter 8) we investigated adherence to inhaled corticosteroids in patients with controlled and uncontrolled asthma who were prescribed high dose inhaled corticosteroids. Non-adherence is known to be a major contributing factor to treatment failure in many chronic conditions. This study confirmed that adherence to ICS is was low in patients with asthma. Remarkably, our study showed lower adherence rates in patients with controlled asthma as compared to those with uncontrolled disease. In addition, adherence rates to ICS were lower in asthma than in COPD, but higher than in other respiratory diseases. In asthma, the only independent factor associated with very poor adherence was being treated in primary care, whereas in mixed asthma/COPD current smoking was the only independently associated factor. These findings confirm that poor adherence is highly prevalent amongst asthma patients, and show that poor adherence is not confined to uncontrolled asthma, but occurs in controlled asthma as well.

GENERAL DISCUSSION

Conclusions and comparison with literature

Adult-onset asthma: subphenotyping and identifying severe disease

The first part of this thesis focused exclusively on patients with late onset asthma and showed that there are several distinct subphenotypes of adult-onset asthma and that severe disease in these patients is associated with active eosinophilic airway inflammation, not only in the peripheral airways' but also in the nose and sinuses. These data fit in with earlier observations in asthma and adult-onset asthma. Previous studies in severe asthma showed that specifically patients with adult-onset disease had higher numbers of airway eosinophils[3;7], were less often sensitized to aeroallergens[3;8] and show a faster decline in lung function[6]. Also, amongst patients with difficult-to-control asthma persistent sputum eosinophilia was associated with late onset disease, persistent airflow limitation and extensive sinus disease[7]. Rhinitis is known to be a predictor of adult-onset disease, even in non-atopic patients[9]. However, the relation between rhinitis and asthma severity is not known. Previously, bresciani et al showed more extensive CT scan abnormalities in patients with severe and/or uncontrolled disease[10], suggesting that there might be a link. In this thesis we showed that there is a high prevalence of sputum eosinophilia and chronic rhinosinusits in patients with adult-onset asthma. In addition, in newly diagnosed adult-onset disease we showed that the extend of CT-sinus deviations in these patients were independently associated with increased percentages of sputum eosinophils. Also, patients with nasal polyposis showed the highest amount of sputum eosinophils and increased sputum eosinophils was independently associated with severe adult-onset disease. Thereby, it could be suggested that there might be a common inflammatory pathway and that this phenotype could develop over time towards more severe disease.

Further evidence for phenotype stability and progression towards less or more severe disease has been shown by a recent study of Boudier et al[11]. They performed a cluster analyses in a group of patients with asthma after a 10-year follow-up period. They showed that 54-88% clusters remained stable over time. Strikingly, there were a few phenotypes that increased in number of patients after the follow up-period. Those with "non-allergic, high symptoms and treatment" and those "non-allergic, moderate symptoms and no treatment". Suggesting that this phenotype indeed can progress over time towards more or less severe. A prospective follow-up study of patients with newly diagnosed asthma could possibly provide extra clues towards the underlying pathophysiology of these changes.

Besides showing an association between severe asthma and eosinophilic disease, we also identified a group of predominantly obese female patients with high symptoms but low

inflammatory markers. In addition, in our cohort we found more females than males with late onset asthma, however female gender was not related to disease severity. A previous cluster analyses in severe asthma also identified a cluster of more obese female patients, although not all patients had adult-onset disease[12]. In addition other studies comparing mild and severe asthma in general, showed more severe disease in females with more neutrophilic inflammation[13]. This suggests that there might be a difference between childhood-onset, which might be complicated by obestity[14], and adult-onset asthma which might be secondary to obesity[15]. Resulting in different phenotypes with different severities.
The results of this thesis support and extend previous studies by showing that there are distinct phenotypes of adult-onset asthma that is consistent in different cohorts[12;16;17]. But also by showing that, as previous suggested, there is a link between adult-onset disease, disease severity and persistent eosinophilia.

Evaluating severe asthma.

Several studies showed that there are many factors associated with asthma control such as race, female gender, younger age, personality traits but also psychopathological factors such as anxiety and depression[18-20]. In addition, it has been shown that these are associated with poor asthma outcomes, increased hospital admissions and emergency department visits[21-24].
In the second part of this thesis we investigated several of these factors associated with disease severity. First, anxiety and depression was associated with prednisone dependent severe asthma as compared to sever non-prednisone dependent or mild asthma. Thereby extending previous results and indicating that in patients with prednisone-dependent disease the co-morbidity anxiety or depression could become a potential factor influencing asthma control. Secondly we showed that that non-adherence is a major problem in the treatment and management of difficult-to-treat airway diseases, irrespective of asthma control and that younger age, treatment by the general practitioner and having controlled disease were independently associated with very poor adherence.
These studies show that physicians should always be aware of factors influencing asthma control and that these are multi factorial and even could be treatment dependent. So when patients experience loss of control adherence should always be checked and in prednisone-dependent patients investigating new co-morbidites is warranted.

Interpretation of the results of the thesis

Adult-onset asthma: subphenotyping and identifying severe disease

There are several underlying mechanisms that could contribute to the subphenotypes described in this thesis. First, the presence of sputum eosinophilia has been associated with a subphenotype of adult-onset asthma in previous studies and could be considered as a key characteristic of the (severe) inflammation predominant phenotype[3;25]. In addition, it has been shown that sputum eosinophilia is consistent over time and in this subphenotype independently associated with extensive sinus disease[7].
The mechanism of the eosinophil infiltration of the bronchial mucosa is believed to be driven by the secretion of interleukins by T_H2-cells when stimulated with antigen, in particular IL-5[26;27]. Through binding to the IL-5 receptor, IL-5 stimulates B cell growth and increases immunoglobulin secretion. This is captured by immunoglobulin receptors present on cells such as mast cells and eosinophils, which release toxic inflammatory molecules that elicit airway obstruction[28]. In addition, IL-5 is also a key mediator in eosinophil activation. The antigens stimulating the T_H2-cells in non atopic asthma are not fully clear, although it is suggested it could be caused by undefined allergies[29] or autoimmunity triggered by viruses[30]. Several studies have shown that eosinophilic airway disease is associated with increased exacerbation and persistent airflow limitation[24;31]. However, the contribution of eosinophils in airway remodelling remains to be established, although it has been demonstrated in mice that accumulation of eosinophils can be responsible for remodelling in a chronic model of asthma[32]. In addition, it is still unclear if this decline in lung function is a result of chronic inflammatory disease or due to recurrent exacerbations. A recent study investigating anti-IL5 in patients with severe eosinophilic asthma showed that treatment with Mepolizumab reduces blood en sputum eosinophils counts and the risk of exacerbations[33;34]. However, a prospective follow-up of these patients is necessary to see whether this positively influences remodelling and lung function decline.

With respect to the second subphenotype, the obese, female asthma subphenotype, studies have shown that body mass index has a strong association with the risk of adult-onset asthma[14;35;36]. Since the prevalence of obesity in the developing countries is increasing, it may be expected that this phenotype will be as well. Several studies found this relationship to be stronger in women than men[37], although this is not a consistent finding. In addition, the mechanistic basis of this relationship has not been identified completely, although there are several mechanical and inflammatory factors suggested that might contribute to the pathogenesis of asthma in these patients. First, obesity has a great impact on lung

mechanics, causing reduced lung volumes and small airway closure[38], thereby increasing the airway hyperresponsiveness and airway smooth muscle stiffness[39;40].
Second, it has been suggested that adipose tissue is metabolically active in inflammation by secreting active cytokines and adipokines, which is believed to be proinflammatory, causing airway inflammation resulting in obesity associated comorbidities and asthma in obese patients[39;40]. Additionally, a recent study showed that markers of metabolic inflammation are indeed significantly higher in obese patients with asthma as compared to controls[41]. However, they showed that airway epithelial cells express receptors for adipokines, suggesting that epithelial cells respond directly to these markers resulting in increased bronchial hyperreactivity[41]. This could explain why "obese asthma" is often associated with low inflammatory markers, as we have shown in our cluster analyses (chapter 3). Last, the comorbidities of overweight may provoke or worsen asthma, in particular gastroesophageal reflux (GERD), sleep-disordered breathing (SDB) or type 2 diabetes[39;42]. Clinically, obesity has been associated with a reduction of therapeutic effect of inhaled corticosteroids with regard to airway inflammation and lung function[43] and a blunted response to dexamethasone[44]. In addition, BMI is increasingly associated with more severe asthma. Although we found a more severe subphenotype of obese asthma, this cluster also included less severe patients. In addition, in our severe asthma study there were no differences in BMI between the patients with severe and milder disease. One explanation might be that non-asthmatic obese adults might gradually develop (mild) asthma due to the pro-inflammatory effects of adipose tissue, whereas patients with severe disease might become obese as a consequence of the use of oral corticosteroids. Thus, a high BMI might be associated with mild as well as severe asthma, via different mechanisms.

Last, we described a cluster of patients with mild-moderate persistent asthma. This group shows that adult-onset asthma is not always severe or uncontrolled, but can also have a milder course and prognosis, suggesting similar mechanisms as the majority of patients with childhood-onset disease.

Evaluating severe asthma

In the second part of this thesis we investigated factors influencing disease severity. First we showed that anxiety and depression are associated with severe prednisone dependent asthma, but not with milder disease. The mechanisms explaining these results could be several and bidirectional. Depression and possibly anxiety are a direct effect of corticosteroid treatment[45-47]. Alternatively, psychological stress might be the cause of prednisone-dependency in patients with asthma. Psychological distress has been shown to be associated with more severe asthma symptoms[48], increased health care utilization[23], and frequent

exacerbations requiring oral corticosteroid bursts[24]. It could be speculated that psychological stress leads to increased perception of asthma symptoms or even more severe airway inflammation[49], which may the cause of failure to control asthma with inhaled medications alone or to discontinue oral corticosteroids after an acute exacerbation. Secondly, we showed that non-adherence is a major issue in controlled and uncontrolled 'severe' asthma and that being treated in primary care and current smoking is associated with non-adherence. It could be speculated that patients in primary care are less intensively monitored and therefore more often non-adherent to their ICS treatment. Alternatively, patients in primary care may have milder disease that can be well controlled on lower ICS doses than originally prescribed.
There are many reasons why a patient could be non-adherent to therapy. Previous studies have shown that reasons for discontinuation are lack of symptoms, doubts about the need for a preventer inhaler, and concerns about potential side effects[50]. Overall, both studies show that there are many factors and mechanisms influencing asthma control, an issue that should continuously assessed in patients with difficult-to-treat disease.

Clinical implications of the thesis

Adult-onset asthma: subphenotyping and identifying severe disease

As awareness of adult-onset asthma increases, a growing number of patients are (correctly) diagnosed with this condition. We now recognize several distinct adult-onset asthma phenotypes with different, severities, co-morbidities and outcome. Also, characterisation of the different phenotypes of adult-onset asthma and the suggested pathophysiological mechanisms will give the opportunity to detect risk factors of severity and poor clinical outcome. Currently, the treatment of asthma, as described in the different international guidelines, is focussed on asthma as a general disease[51,52].
Our results show several different subphenotypes of adult-onset asthma, for which an extension towards more personalized medicine could be more beneficial. In patients with the non-atopic, inflammation predominant asthma subtype special attention should go out to assessment of sensitization to molds and aspergillus fumigatus, as it has been associated with an increased risk for adult-onset asthma and reduced lung function[53-55]. Furthermore, assessment of small airway disease, presence of (persistent) eosinophilia in blood and if possible sputum is important. Additional, patients who do not report nasal symptoms often appear to have sinonasal disease. Therefore sinonasal assessment by means of CT-scanning or nasal endoscopy is also warranted, as it has been suggested that most patients benefit from reducing sinonasal inflammation[56]. In addition, as small airway's disease is more common in these patients, ultrafine particle inhaler could be of more benefit in gaining more asthma control. Lastly, several studies now showed promising results in reducing

exacerbations and eosinophil counts when treating these patients with the monoclonal antibody mepolizumab[33;34;57].

In patients with the obese female preponderant asthma subtype waist circumference should be assessed because it is associated with asthma severity[58], and physicians should be especially aware of the comorbidities that may worsen this type of asthma, such as gastroesophageal reflux (GERD)[39], sleep-disordered breathing (SDB)[39] or type 2 diabetes[42]. When treating these patients special attention should go out to weight reduction as it often improves asthma severity and control[59]. Last, our results show that not all patients with adult-onset asthma have severe disease. Therefore, clinicians should be aware that at diagnosis a patient could become severe, but that this is not always the case. Thorough investigation towards factors associated with disease severity and closely monitoring is warranted to hopefully prevent severe disease and lung function decline.

Evaluating severe asthma

With respect to the second part of this thesis there are also several clinical implications. First we showed that anxiety and depression is associated with prednisone dependency and therefore especially these patients should be screened routinely. In addition, with respect to adherence, the clinician should be aware that most patients are not using their inhaler medication according to prescription, before starting with oral corticosteroids or other novel therapies, especially when asthma is treated by the general practitioner.

Future directions

Adult-onset asthma: subphenotyping and identifying severe disease

During the discussion of this thesis, several aspects have been highlighted with regards to future research, but there is much more work to be done.

With respect to basic science there is more research needed towards the role of the eosinophil in severe late-onset disease, especially with respect to its role in asthma onset, airway remodelling, lung function decline but also towards its link between the nose and the lower (small) airway's. Secondly, there is still uncertainty with respect to the mechanisms of obesity associated late onset disease, such as the specific role of adipokines in the development of asthma, but also the remission of asthma after weight loss. It is well known that obesity leads towards increased adipokines[59]. However, if they increase bronchial hyperreactivity by directly influencing the epithelial cell, this could explain the absence of inflammatory cells and the improvement of asthma severity after weight loss. But this still needs to be investigated. In addition, not all patients improve after weight loss, nor have

low inflammatory markers. Another question that is still unanswered is the role of genetic and/or environmental predisposition in the development of adult-onset disease. In asthma in general there is a link between ADAM-33 and the development of asthma. However, adult-onset asthma typically does not run in families, but could there be a genetic predisposition?
The next step is to implement these results into translational research, combining the basics in the clinical patient, however clinical studies investigating development of adult-onset asthma are also warranted. There is a need for prospective follow-up studies starting from the onset of adult-onset asthma until stable disease, preferably including genetics, bronchial biopsies and sputum and blood cell counts. This type of research will give the opportunity to assess the natural course of different subtypes of adult-onset asthma and investigate the pathophysiological mechanisms, in particular the role of environmental influences, respiratory infections and the development of comorbidities
In clinical research, future research should aim for increasing insights in asthma development after the onset of disease, focus on the differences between the different subphenotypes and the results of personalized therapies in these subsets of patients. In addition, several novel targeted therapies are showing promising results in patients with severe eosinophilic disease[33]. Patients using these novel therapies should be closely monitored to investigate the long-term results in improvement of quality of life, disease severity, airway remodelling and lung function decline, but also (new) co-morbidities and side-effects.
Last, there is an ongoing need for the development of new targeted therapies. Not all patients respond to standard treatment and targeted therapies are appropriate for specific subphenotypes. Combining basic, translational and clinical research will help to give directions towards this research goal.

Evaluating severe asthma

With respect to factors influencing asthma control, this is an ongoing process in which further research is continuously needed. In patients with prednisone dependent asthma interventional studies investigating if treatment of anxiety and/or depression would be successful in gaining more asthma control are necessary. In addition, further research is warranted in tapering oral corticosteroids and the development of new therapies with less side effects, that hopefully make oral corticosteroids redundant. Also, further research is warranted in factors associated with adherence to treatment regimens, especially in patients with uncontrolled disease. In addition, interventional studies are needed investigating methods for improving adherence and maintaining a correct inhalation technique.

Final remarks

In this thesis we investigated and associated several new insights into disease severity in adult asthma. First we identified several clusters of adult-onset asthma and in addition to this we showed that severe disease is mostly associated with persistent eosinophilia and ENT disease. Also we showed that there are several factors that influence disease severity. However, more research is warranted in these patients, especially in identifying the underlying pathofysiology.

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Chapter 10

Samenvatting

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NEDERLANDSE SAMENVATTING

Astma is een chronische ontsteking van de luchtwegen waardoor de luchtwegen (wisselend) vernauwen wat zich kan uiten in hoesten, kortademigheid en een piepende ademhaling. Er zijn veel verschillende prikkels die deze ontstekingsreactie kunnen uitlokken bijvoorbeeld allergieën voor onder andere huisstofmijt, pollen of huisdieren. Er zijn ook niet-allergische prikkels die deze ontstekingsreactie kunnen uitlokken zoals mist, rook of inspanning. Astma kan voorkomen bij alle mensen wereldwijd en in alle leeftijdsgroepen. Ongeveer 5-10% van de mensen met astma hebben ernstig astma die ernstige comorbiditeit en verminderde kwaliteit van leven met zich meebrengt. Recente studies hebben laten zien dat er verschillende subtypes van astma zijn, een belangrijk onderscheid dat hierbij gemaakt kan worden is of de astma op kinderleeftijd ontstaan is of pas op volwassen leeftijd, het zogenaamde 'laat astma'.

Deel 1: 'Laat astma': subfenotypering en het identificeren van ernstig astma.

Hoofdstuk 2 is een review van de literatuur tot nu toe over 'laat astma' met als doel een overzicht te geven van de incidentie en prevalentie van 'laat astma' en van studies die verschillende klinisch herkenbare fenotypes van deze ziekte. In dit hoofdstuk laten we zien dat de incidentie van 'laat astma' geschat is op ongeveer 4.6/1000 per jaar voor vrouwen en 3.6/1000 per jaar voor mannen. De prevalentie van 'laat astma' is onbekend, hoewel sommige studies in ernstig astma laten zien dat 'laat astma' tot wel 50% van de ernstig astma patiënten kan betreffen. Ook zijn er verschillende etiologische factoren een risico zijn voor het ontstaan van 'laat astma', zoals beroeps gebonden factoren, roken, overgewicht en virus infecties. Recent hebben enkele cluster analyses in (ernstig) astma verschillende subgroepen van 'laat astma' laten zien zoals een groep niet-allergische patiënten met veel ontstekingcellen en slechtere longfunctie en een groep van voornamelijk vrouwen met overgewicht en veel klachten. Als laatste hebben we gekeken naar de behandeling van ernstig 'laat astma'. Hier laten we zien dat in het algemeen de behandeling van 'laat astma' gelijk is aan astma dat op kinderleeftijd ontstaat, maar dat hierbij een meer persoonlijke aanpak nodig is afhankelijk van het subtype.

In hoofdstuk 3 beschrijven we en populatie van 200 patiënten met astma die op volwassen leeftijd ontstaan is. Op de data die we bij deze patiënten verzameld is hebben we een cluster analyse uitgevoerd waarbij we gekeken hebben of er verschillende fenotypes te identificeren zijn. Hierbij vonden we 3 verschillende subgroepen met een duidelijk verschil in klinische en ontstekings kenmerken. De eerste groep bestond uit patiënten met ernstige eosinofiele ontsteking met persisterend een slechtere longfunctie maar weinig klachten van hun

astma. De tweede groep werd gekarakteriseerd door vooral vrouwen met overwicht met frequent astma symptomen en een hoge mate van zorgbehoefte (ziekenhuis bezoek), maar een normale longfunctie en weinig inflammatie in de longen. De laatste groep bestond uit patiënten met mild tot matig ernstig astma, met weinig symptomen.
In hoofdstuk 4 hebben we 78 patiënten met ernstig astma vergeleken met 98 patiënten met mild astma. Daarin laten we zien dat patiënten met ernstig astma vaker KNO klachten hebben en neuspoliepen en ondanks behandeling meer eosinofiele (ontstekings) cellen in de longen. Deze studie suggereert dat 'laat astma' een specifiek fenotype is met een andere pathofysiologie dan mildere vormen van deze aandoening, maar ook vergeleken met astma in het algemeen.
In hoofdstuk 5 hebben we gekeken naar het voorkomen van chronische rhinosinusitis (bijholteklachten, CRS) bij patiënten die recent de diagnose 'laat astma' hebben gekregen (<1 jaar) en hebben daarbij gekeken of het geassocieerd is met meer eosinofiele ontsteking in de longen. Deze resultaten laten zien dat veel patiënten CRS klachten hebben als de diagnose astma wordt gesteld. De patiënten met neuspoliepen hadden de hoogste hoeveelheid aan eosinofiele cellen in de longen en meer afwijkingen op de CT scan die gemaakt werd van de sinussen.
In hoofdstuk 6 hebben we gekeken naar factoren die geassocieerd zijn met afname van de longfunctie in 'laat astma'. Deze studie was gebaseerd op een eerdere studie in patiënten met moeilijk behandelbaar astma, welke liet zien dat patiënten met 'laat astma' een snellere daling in long functie laten zien dan patiënten met astma dat ontstaan was op kinderleeftijd. In onze studie lieten we zien dat het mannelijke geslacht en afwezigheid van allergieën onafhankelijk geassocieerd zijn met persisterende luchtweg obstructie, onafhankelijk van leeftijd, body mass index (BMI) of rookverleden.

Deel 2: Evaluatie van ernstig astma.

In het tweede deel van dit proefschrift hebben we gekeken naar specifieke factoren die de ernst van astma en astma controle beïnvloeden. Eerdere studies hebben laten zien angst en depressie veel voorkomen bij patiënten met astma, maar er is geen duidelijke relatie met de ernst van de ziekte. Daarom hebben we in hoofdstuk 7 gekeken naar angst, depressie en persoonlijkheidskenmerken in patiënten met mild, ernstig en ernstig prednison-afhankelijk astma. In deze studie vonden we significant meer angst en depressie in patiënten met prednison afhankelijk astma in vergelijking met patiënten met niet prednison afhankelijk ernstig astma of mild astma. Dit suggereert dat niet de ernst van astma maar de behandeling met orale corticosteroïden is geassocieerd met psychologische bij effecten, zoals angst en depressie.

In de laatste studie in dit proefschrift (hoofdstuk 8) onderzochten we therapietrouw in patiënten met astma welke onder controle is en welke niet onder controle is (>2 exacerbaties per jaar, veel symptomen of minstens 1 ziekenhuisopname in het afgelopen jaar) met een voorschrift voor hoge dosis inhalatie corticosteroïden. Therapie ontrouw is een bekende factor die bijdraagt aan het falen van de behandeling in veel chronische ziekten. De studie in hoofdstuk 8 bevestigde dat therapietrouw laag is in patiënten met astma. Opvallend was dat patiënten met gecontroleerd astma nog minder therapietrouw waren dan patiënten met ongecontroleerd astma. Ook laat deze studie zien dat therapietrouw lager is in patiënten met astma vergeleken met COPD, maar hoger dan de groep patiënten met andere longziekten. In patiënten met astma was behandeling bij de huisarts geassocieerd met minder therapietrouw en in gemixt astma/COPD was dit geassocieerd met roken. Deze studie bevestigen dat therapie ontrouw veel voorkomt onder patiënten met astma en laat zien dat dit niet alleen voorkomt bij ongecontroleerd astma.

Dankwoord

DANKWOORD

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Tot slot wil ik Hem bedanken aan wie ik alles te danken heb! Fil.4:13.

Curriculum Vitae

CURRICULUM VITAE

Marijke Amelink werd geboren op 8 januari 1982 te Leeuwarden. In 2000 haalde zij haar VWO diploma aan het Liudger College te Drachten. Daarna is zij begonnen aan de opleiding pedagogiek aan de Rijks Universiteit Groningen tot zij in 2001 werd ingeloot voor Geneeskunde. In 2008 haalde zij haar arts examen waarna zij 1 jaar heeft gewerkt als arts niet in opleiding in het Medisch Centrum Leeuwarden op de afdeling Longziekten. In 2009 is zij begonnen aan haar promotieproject in het Academisch Medisch Centrum in Amsterdam op de afdeling longziekten. Sinds 1 april 2013 is zij werkzaam als longarts in opleiding in het Academisch Medisch Centrum, Amsterdam.

Portfolio

PORTFOLIO

	Year	ECT
Specific courses:		
Respiratory Research School Davos	2009	1
Respiratory Research School Davos	2010	2
Monitoring airway disease, ERS, Amsteram	2009	0.75
Small airway disease, ERS, Amsterdam	2011	0.75
Seminars		
Lung Amsterdam	2009, 2010	0.4
Lung Amsterdam, mini symposium	2009, 2010	0.4
Presentations		
ATS, Toronto, Canada. Poster presentation: psychopathologie in mild versus severe corticosteroid dependent asthma.	2008	0.5
ATS, San Diego. Poster presentation: Assessment of exhaled breathprints by electronic nose before and after use of Salbutamol in asthmatic patients	2009	0.5
ATS, New Orleans. Poster presentation: Male gender and absence of atopy are associated with persistent airflow limitation in adult onset asthma.	2010	0.5
ERS, Barcelona. Poster discussion: Male gender and absence of atopy are associated with persistent airflow limitation in adult onset asthma.	2010	0.5
ATS, Denver. Oral presentation: 'Nasal polyposis identifies an at risk phenotype of patients with adult-onset asthma'	2011	0.5
ERS, Amsterdam. Oral presentation: 'The role of food allergy in adult-onset asthma'	2011	0.5
ERS, Wenen. Poster presentation: 'Phenotypes of Adult-onset Asthma by Cluster Analysis'	2012	0.5
ATS, San Francisco. Abstract: 'Severe adult-onset asthma, a distinct phenotype'.	2013	0.5
Internation Conferences		
Astmafondsdag	2009	0.5
International conference, ERS	2010, 2011, 2012, 2013	4
International conference, ATS	2009, 2010, 2011, 2013	4
Netherlands respiratory society, NRS	2010, 2011	2
Research seminar, ERS, Estoril	2013	1
Student teaching	2012	1
Other		
Journal club	2009-2012	4

Insights into disease severity in adult asthma