Asthma control: Patient and environment

Rijssenbeek-Nouwens, Lous

ASTHMA CONTROL

PATIENT AND ENVIRONMENT

Lucia H.M. Rijssenbeek-Nouwens

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Faculteit der Geneeskunde

Voor alle patiënten

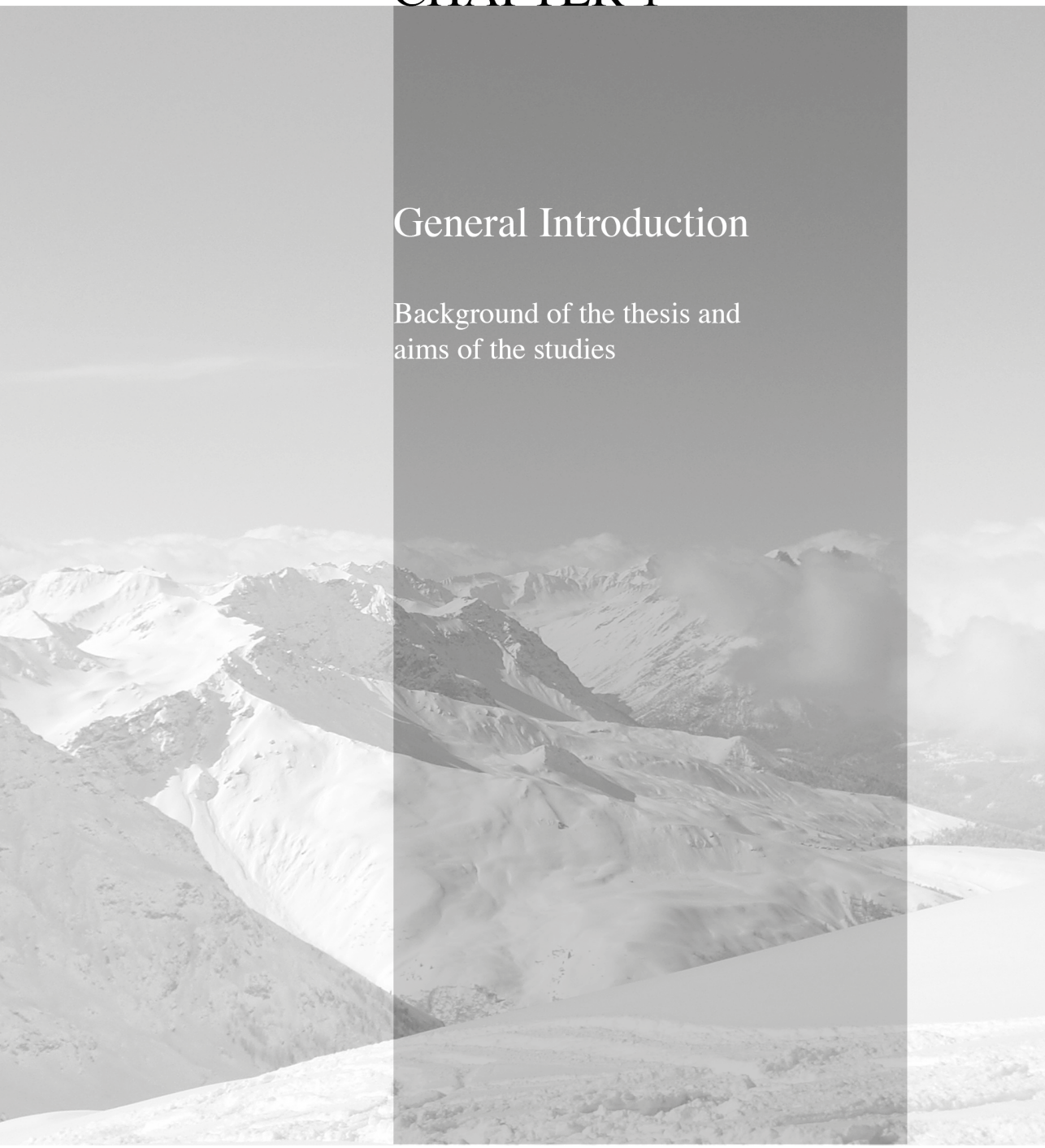
met ernstig en moeilijk te controleren astma

Contents

CHAPTER 1

General Introduction

Background of the thesis and aims of the studies



Asthma

Asthma is defined as a chronic disorder of the airways characterized by inflammation, airway hyper-responsiveness, variable narrowing of the airways and symptoms of shortness of breath, wheezing and coughing [1].

Asthma is a major cause of disability, poor quality of life and health resource utilization throughout the world, affecting an estimated 315 million persons of all ages [2]. The socioeconomic consequences of asthma, both in terms of direct medical and nonmedical expenditures are impressive [3, 4]. Asthma costs correspond directly with asthma control, rising to four times in uncontrolled asthma [5, 6]. Despite the development and availability of powerful medications, the burden of uncontrolled asthma is immense for the patients, for the caregivers and the community [7-9].

The diagnosis of asthma is primarily based on a typical history and confirmation of variable airflow obstruction [10]. However, there is now increasing evidence that asthma is a heterogeneous disease with a variety of phenotypes, resulting from complex interactions between genetic and environmental factors [11-14]. The type and intensity of airway inflammation varies between phenotypes, and results from an altered or excessive response of the airways epithelium to environmental trigger factors [15].

Asthma control

Asthma control is the goal of asthma treatment, since asthma cannot be cured. Asthma control is defined as the extent to which the various manifestations of asthma have been reduced, incorporating components of current control as well as future risks [16]. Good current control implies absence of symptoms, normal lifestyle and activity levels, minimal airway obstruction and minimal use of rescue bronchodilators. The Global Initiative for Asthma (GINA) Guidelines have established 3 levels of asthma control: (well) controlled, partially (not well) controlled and (very poorly) uncontrolled [1]. The GOAL (Gaining Optimal Asthma Control) study showed the possibility to achieve control of asthma in patients with a wide range of asthma severity [17].

Assessment of asthma control

Unfortunately, up to now, no ideal indicator for asthma control exists. There is no exhaustive test such as for example hemoglobulin A_{1C} used for the assessment of control of diabetes mellitus. Good asthma control means for the patient having no symptoms, no exacerbations and no limitations in daily life and is usually assessed by the Asthma Control Questionnaire (ACQ) [18-20]. Asthma is considered uncontrolled when the ACQ score is greater than 1.5 [20].

Assessment of asthma control is recommended to include four domains: 1. patient-reported symptoms (ACQ), objective measurement of 2. lung function, 3. Airway hyper responsiveness and 4. inflammation of the airways [16]. The challenge for the future is to develop a framework for optimal assessment of asthma control considering these four domains. However, this is likely not the final answer, because new insights related to specific molecular pathways of different asthma phenotypes will probably lead to more accurate ways to monitor disease activity and achieve total asthma control.

Asthma control versus asthma severity

While asthma control involves mastering illness symptoms and future risks, asthma severity reflects the activity of the underlying disease state, which depends on the underlying genotype and endotype, co-morbidities, and environmental and patient related factors [21,22]. The early GINA guidelines initially suggested to base asthma treatment steps on the severity of patient's asthma before initiating any treatment.

Gradually, the base and goal of treatment have been shifted towards control of asthma. This means that nowadays asthma severity is defined on the intensity of treatment required to achieve good control of asthma[16].

Severe asthma is now defined as asthma that requires high intensity treatment to prevent it from becoming uncontrolled or asthma remaining uncontrolled despite this therapy [23]. High intensity treatment in adults is defined as over 1000 µg/day of fluticasone equivalent and/or daily oral steroids, combined with long acting beta2 agonists [23, 24]. The severity of asthma is a relatively stable component that may slowly change over time. However, the level of asthma control may vary from day to day, or week to week, reacting on exposure to environmental triggers, virus infection or changes in treatment adherence [21].

Impact of asthma control on future risks

Current good control of asthma is necessary for reduction of future risks and for patient health status (see table 1). Future risks consist of: worsening of asthma symptoms, exacerbations, lung function decline and adverse effects of high dose asthma medication[16, 25].

Poor asthma control has profound impact on several domains of a patient's health status [26-28]. Poor health status has been associated with developing stress, anxiety disorders and depression, lower cognitive function and learning disability [29-33].

On the other hand, good asthma control is associated with better health status, improved lung function, and reduced exacerbation rate [25, 34].

Table 1 | current asthma control and future risks [25]

Control of asthma		↔	**Future risk**	
Symptoms (ACQ)	Reliever use		Worsening of symptoms	Exacerbation
Activity level	Lung function		Lung function loss	Adverse effects of medication

Table 2 | Factors associated with poor asthma control

Patient related factors	**Environmental factors**
Adherence to medication [37, 38]	Allergens [58-66]
Coping with asthma [29]	Viruses[67, 68]
Psycho-social factors [46-49]	Outdoor air pollution [79-84]
Smoking habits [69, 73-75]	Indoor air pollution [78]
Comorbidities [36]	(Passive) smoking [97, 98]
Drugs [94-96]	Respiratory irritants [99]
	Occupational agents [100, 101]
	Stressful events [31, 89-91]

Factors associated with asthma control

Despite International Guidelines and the availability of powerful medications, control of asthma proves difficult to achieve [7-9]. One study showed that six out of seven European patients with asthma, using inhalation corticosteroids, did not achieve good asthma control [35]. Patient-related factors such as poor inhalation technique, non adherence to treatment and inadequate coping techniques are important contributing factors although other patient related and environmental triggers may play even a more important role (see table 2). Therefore in this thesis we studied the role of some important patient related factors as well as environmental exposures in uncontrolled asthma.

Patient related factors

Adherence to treatment

Non adherence to anti-inflammatory treatment is an often mentioned cause of poor asthma control[37]. Adherence refers to the extent to which the patient's behaviour matches agreed recommendation from the prescriber of therapy[38]. Most people do not strictly follow treatment recommendations. Patients tend to evaluate whether the treatment advice is in line with their personal experiences, fears, understanding and beliefs about their illness and medication and subsequently make their own decision [38,39]. It is not easy to assess adherence. Not only do most of the patients with asthma overestimate their adherence, also clinicians tend to overestimate patient adherence.

Possible methods for measuring patient adherence are clinical judgement, self-report, medication measurement, pharmacy database-review, electronic medication monitors or the FeNO suppression test by direct observed inhaled steroid treatment [40-42]. Prevalence rates of non-adherence vary from 35 to 65% in different studies [43,44].

Coping with asthma

Coping with an unpredictable disease as asthma is a burden for life. This burden influences patient's life significantly and is affected by personal coping strategies which can result in a psychological dis-balance.

Uncontrolled asthma, especially exacerbation of asthma, is a high burden for psychosocial health, since patients have to manage their asthma and cope with the consequences in daily life [45]. Psychological distress and decreased feelings of control were significantly more frequent in subjects with asthma in population based studies [28,30] Appropriate coping strategies are dependent on personal factors. Strategies for coping can be rational or either emotional. These strategies can lead to frustration, depression and anxiety and result in an impaired health status [46-49].

Psychological factors influencing asthma control

Psychological co-morbidities can influence negatively asthma control. Psychological problems are often unrecognized and untreated in asthma patients and have been found to be associated with poor asthma control[50- 52]. For example, since depression is associated with decreased problem solving capabilities, it can influence decision making and proper coping strategies of people with asthma [28]. Although no significant differences in psychological characteristics were found between patients with mild and severe asthma, psychopathology in patients with severe asthma is associated with increased health care utilization [53-56].

Environmental factors

Specific environmental factors negatively affect asthma control. Exposure to allergens in sensitized patients can lead to an immediate and a delayed, prolonged asthmatic reaction [57]. These reactions lead to enhanced airway hyper-responsiveness and airway eosinophilic inflammation. Also exposure to so-called nonspecific triggers such as smoke, stress and air pollution, may leads to enhanced hyper-responsiveness and airway inflammation resulting in loss of asthma control [72, 74, 76, 84, 89.]

Allergens

Numerous community studies show that control of asthma is associated with exposure to indoor allergens [58] . House dust mite (HDM) allergens are a major cause of asthma worldwide [59]. House dust mite exposure can provoke loss of asthma control leading to exacerbations and prolonged exposure can lead to persistence of symptoms [59,60]. Repeated low-dose allergen exposure in asthma increases airway inflammation even without worsening of symptoms[61]. Also direct and indirect exposure to pet allergen exacerbates symptoms [62]. Exposure to fungi in sensitized patients may be another cause of loss of asthma control. A close association between fungal sensitization and asthma severity has been found in adults and children [63-65]. When fungi colonize the respiratory tract they may provide a chronic source of allergen exposure, which may influence clinical features [66] . Moreover, exposure to a combination of allergens and viruses may result in severe exacerbations and hospital admissions [67,68] .

Smoking

About 25 % of patients with asthma are regular smokers [69] . In the Netherlands even 27% of patients with asthma keep smoking[70]. Active cigarette smoking impairs the efficacy of inhaled corticosteroids, one of the reasons for uncontrolled asthma in smokers [71, 72] . Asthma patients who smoke have often more severe asthma symptoms, an accelerated decline in lung function over time, increased hospital based care and mortality than non smoking asthmatics[73-75] . Current smokers with severe asthma exhibit worse clinical outcomes

compared to ex-smokers and never smokers with severe asthma, as was demonstrated in a recent study [76]. Passive smoking is also related to more uncontrolled asthma [77].

Air pollution

Mounting evidence suggests the negative effect of air pollution on respiratory health [78]. Air pollution induces increased airway inflammation and airway hyper-responsiveness, and leads to uncontrolled asthma[79]. Exposure to particulate matter ($PM_{3,10}$) and volatile organic compounds (NO_2 and O_3) is associated with more asthma symptoms, increased risk of hospitalizations and ICU admissions in children [80-82]. In adults, different levels and duration of exposure to air pollution are associated with reduction in lung function, more airway inflammation, loss of asthma control, exacerbations and even death [83, 84]. Long-term exposure to air pollution can contribute to new-onset asthma in both children and adults [83, 85].

Moreover the presence of air pollution can enhance the allergic reaction as well as the viral infection leading to hospitalization for asthma [86, 87].

Especially children, adults with severe asthma and persons living near roads with high vehicle traffic are at increased risk of adverse effects from exposure to air pollution [79, 88]. Taken together, air pollution constitutes an inconvenient and complex environmental factor that is associated with loss of asthma control.

External stressful factors

Acute and chronic stress, such as specific life events and traumas, offer additional challenges to asthma control. A number of studies illustrates a model in which psychological stress amplifies the immune system and alters the airway inflammatory response to irritants, allergens and infections [89]. For example, a study in students showed that school examinations enhance airway inflammation to allergen challenge [31]. In children, severely negative life events increase the risk of asthma attacks over the weeks that follow the event. This risk is magnified and brought forward in time if the child's life situation is also characterised by multiple chronic stressors [90]. Moreover, chronic stress is associated with reduced responsiveness to corticosteroids [91].

Corticosteroids as psychological aggravating factor

Asthma medication, in particular oral corticosteroids, can have psychological and cognitive side effects. Psychiatric side effects from corticosteroids are commonly reported and include mania, depression and mood disturbances. Psychiatric symptoms usually occur within two weeks of CS treatment and seem to be dose dependent [92]. A study showed that patients with severe, prednisone-dependent asthma have more often depression and anxiety symptoms as compared to patients with severe non-prednisone dependent or mild-moderate asthma [93].

Relationship between asthma control and potential contributing factors in this thesis

In patients with uncontrolled asthma, assessment of specific individual and environmental factors is crucial. For that purpose, an algorithm based on international consensus can be used, which offers a stepwise approach to address several of these factors [24, 102]. However, a complete evaluation of the complex interaction between the different factors is still extremely difficult. Therefore, in this thesis, we focussed on selected factors related to asthma control. Including adherence to medication, assessment of health status and avoidance of house dust mite. Furthermore, we studied the effects of high altitude treatment, an attractive example of multidimensional treatment in a trigger-free environment.

Non-adherence

Addressing non-adherence is supposed to deliver greater benefit in uncontrolled asthma than any novel treatment [103]. Adherence is a modifiable behaviour, rather than a fixed characteristic and therefore effective interventions are needed [104].

However, adherence intervention studies show that effective interventions remain elusive [105, 106]. There are still many unknown aspects of adherence. Therefore, we investigated the prevalence of non-adherence to inhaled corticosteroids in patients with asthma and high intensity asthma treatment and compared adherence rates amongst patients with controlled and uncontrolled asthma.

Coping and psychosocial factors

The relation between coping, control of asthma and psychosocial factors is complex. A growing body of literature shows contributory influences of psychosocial factors on patients' experience of asthma and how they cope with and manage their asthma [107]. However, the direction of the interplay between asthma and psychosocial factors has not been confirmed. It has even been suggested that asthma itself and psychosocial factors can be influenced by each other [108]. The burden of uncontrolled asthma affects health status and may be influenced by patient characteristics such as coping strategies, subjective impairment, emotions and behavioural impairments. Further research is needed to assess the impact of poor asthma control on these different domains of health status and to disentangle the complexity of the interaction of different domains. Therefore we studied the usefulness of the Nijmegen Clinical Screening Instrument (NCSI) in measuring health status in patients with uncontrolled asthma.

Environmental control: Allergen avoidance

Allergen avoidance as strategy to improve asthma control was suggested since the recognition of the role of HDM allergen in asthma [109, 110]. In studies on the effect of low mite allergen environments such as a hospital setting or at high altitude, control of asthma improved not only symptomatically but also in terms of airway hyper-responsiveness[111, 112]. The question was then raised whether a major reduction in personal exposure, similar to that at high altitude, could also be achieved in homes at sea level [113]. This stimulated researchers to develop methods to reach and maintain a dust free environment in homes of HDM sensitized patients. Some methods of allergen avoidance did indeed lead to reduction in allergen exposure and showed clinical benefit, others proved to be ineffective [114, 115].

Avoidance studies were generally performed in relatively mild asthmatics and only a few avoidance studies were subjected to a randomized controlled study design[116]. The effect of avoidance of HDM allergen at sea level on asthma control in patients with more severe asthma is unknown. Therefore we evaluated the effect of a targeted mono-intervention reducing HDM level, on asthma control and on allergen-specific parameters.

Environmental control: Reducing exposure to air pollution

In the light of the detrimental effects of air pollution in vulnerable patients, reduction of exposure to air pollutants may entail positive respiratory health effects. Small improvements in respiratory function were indeed found even after a modest decrease in outdoor air pollution within 2 years of traffic reducing policy in the Netherlands [117]. Gradual decreases in particulate levels over 11 years were associated with attenuation in age related lung function decline and respiratory symptoms among randomly selected adults in Switzerland [118]. Moving to a cleaner area with less air pollution showed to improve lung function growth in adolescents within 1 to 3 years [119]. Moreover a short reduction in air pollution during one week showed to be associated with reduction in airway inflammation, measured by exhaled nitric oxide in children normally living in a highly polluted inner city [120]. These studies show that reduction in air pollution is associated with improvement of respiratory health. However, no direct information is available on the effects of air pollution on asthma control. The Merem Dutch Asthma centre Davos is situated at high altitude with very little air pollution [121]. In this thesis we conducted a study to see if high altitude treatments leads to better control of asthma.

Identification of patient and environmental factors for adequate treatment of uncontrolled asthma

Uncontrolled asthma can further deteriorate due to many personal and environmental factors, as above mentioned. Assessment of both patient related and environmental factors may give insight into the complex interaction between these factors and how they may lead to uncontrolled asthma. With an individualized asthma self-management plan the patient will be taught a coping strategy based on self-control of disease leading to improvement of asthma control and adherence to medication[122]. However, besides patient related factors also environmental factors should be addressed and removed if possible.

High altitude treatment implies multidisciplinary and multidimensional treatment by a team of asthma experts. This treatment is based on addressing patient related factors in a low trigger environment with good air quality. The high altitude environment in Davos is characterized by relatively dry air, which is responsible for the reduced levels of HDM and fungi [110]. However, there are more favourable factors that characterize the high altitude environment. The geographical location of Davos, far away from the nearest industrial area, ensures clean air with remarkably low exposure to air pollution [121]. Moreover, the Merem Dutch Asthma centre Davos is a strictly smoke free clinic. This low trigger environment might reduce airway inflammation and airway hyper-responsiveness even in patients with non-allergic uncontrolled asthma. Therefore, we studied the effect of high altitude treatment on asthma control in patients with uncontrolled allergic and non-allergic asthma.

Aims of the studies

The studies of this thesis focus on patient related and environmental factors and interventions in relation to asthma control.

- In the first study (*chapter 2*) the prevalence of non-adherence to inhaled corticosteroids in patients with controlled and uncontrolled asthma was assessed.
- In *chapter 3* we investigated the suitability of the Nijmegen Clinical Screening Instrument (NCSI) for measuring different domains of health status in patients with uncontrolled asthma. The outcome of this instrument can give valuable insights into patients' coping strategies.
- In *chapter 4* we explored the effect of reduced exposure to house dust mite, the most important environmental aggravating factor in sensitized patients with moderate to severe asthma, by a single intervention of impermeable mattress covers.
- In *chapter 5* we studied the effect of anti-allergic mattress covers on house dust mite-induced early- and late-airway reactions in order to collect information on the underlying mechanisms, such as allergen sensitivity and inflammation.
- *Chapter 6* gives an update of the role and usefulness of anti-allergic mattress covers in the treatment of asthma to provide more insight into the evidence of allergen avoidance measures.
- *Chapter 7* is a review article about the effects of high altitude treatment on asthma control in children and adults. In addition to the known low levels of house dust mite, also other beneficial features of the mountain climate are discussed.
- The purpose of the study in *chapter 8* was to investigate whether high altitude treatment was equally effective in improving asthma control in severe asthmatic patients with or without house dust mite allergy and with or without any allergies.
- In *chapter 9*, the results of the previous studies are summarized and the implications are discussed from clinical and research perspectives.

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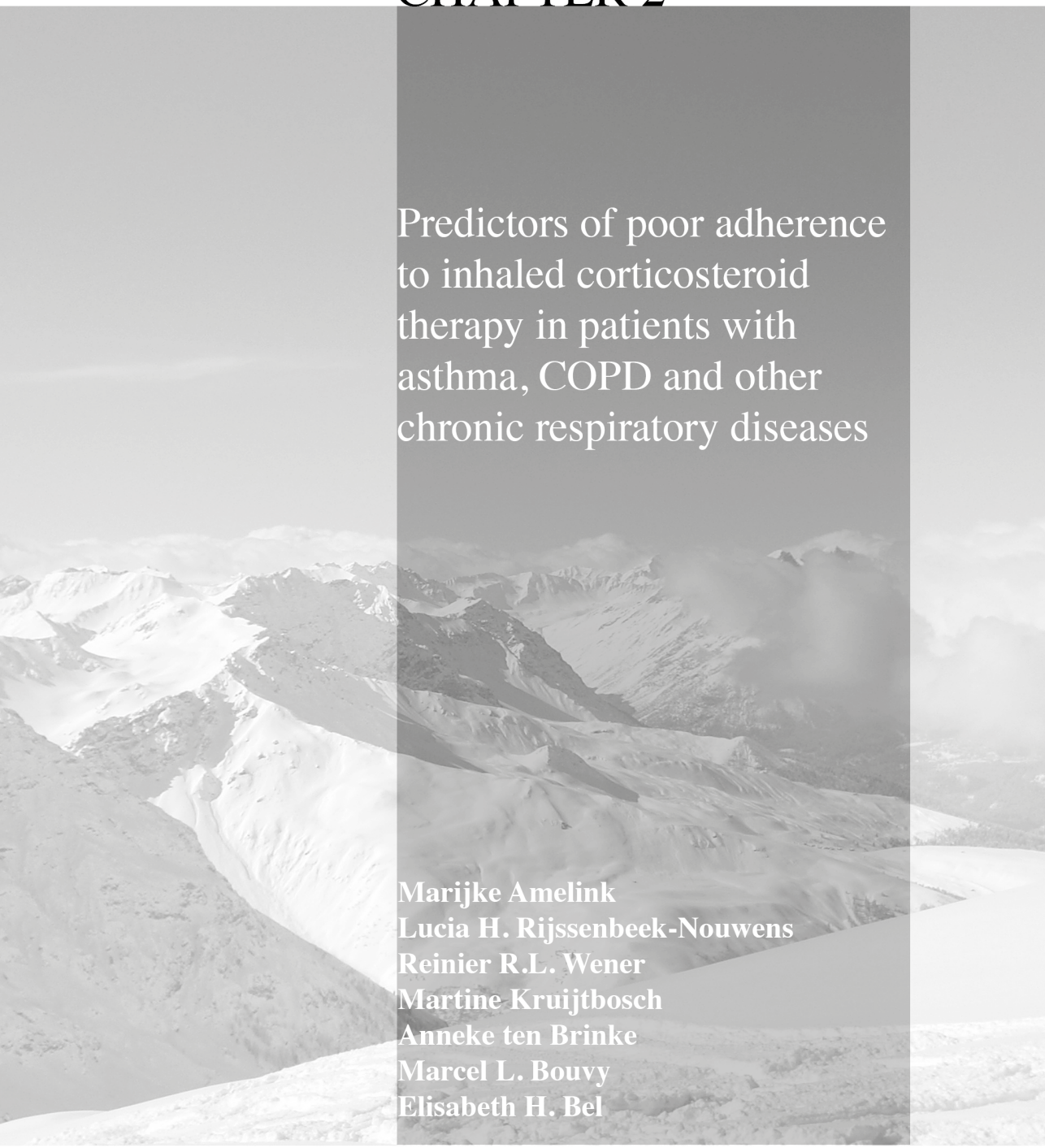
CHAPTER 2



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

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Abstract

Background

One of the major causes of treatment failure in respiratory diseases is non-adherence to treatment. Adherence rates in patients with severe airway disease are scarce.

Aim

To assess the prevalence of non-adherence to inhaled corticosteroids in a large cohort of primary and secondary care patients with high intensity treatment. To compare adherence amongst patients with controlled and uncontrolled disease, and between asthma and other respiratory disorders. Last, to identify factors associated with non-adherence.

Methods

All patients (>18yr) prescribed ICS 1000ug fluticason eq. or 500ug plus chronic oral corticosteroids were selected from 47 community pharmacies. Data contained all prescription drugs dispensed in 2011. Patients were asked to complete questionnaires on demographics and the Asthma Control Questionnaire. Adherence was defined as very poor (<50%), poor (50-80%), adherent (80-100%) or overuse (>100%).

Results

1850 out of 5002 patients completed the questionnaires of which 40.8% was diagnosed with asthma, 29.2% mixed asthma/COPD and 22.6% COPD. Adherence rates were lower in asthma than in COPD, but higher than in other respiratory diseases. Also, adherence rates were lower in patients with controlled asthma as compared to uncontrolled disease. Amongst all patients younger age, treatment in primary care and controlled disease were independently associated with non-adherence. In asthma was being treated in primary care the only independent factor associated with very poor adherence, whereas in mixed asthma/COPD current smoking was independently associated.

In conclusion

Non-adherence is a major problem in the treatment and management of difficult-to-treat airway diseases as the majority of patients are non-adherent, irrespective of asthma control. Therefore, medication prescription refills should be checked when a patient has loss of control or before considering intensifying or adapting treatment.

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 year 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. An 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 [12] 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 2017 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.

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 392 (21.2%) uncontrolled disease). Four hundred nineteen patients

(22.6%) had COPD and 137 (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 per cent 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.

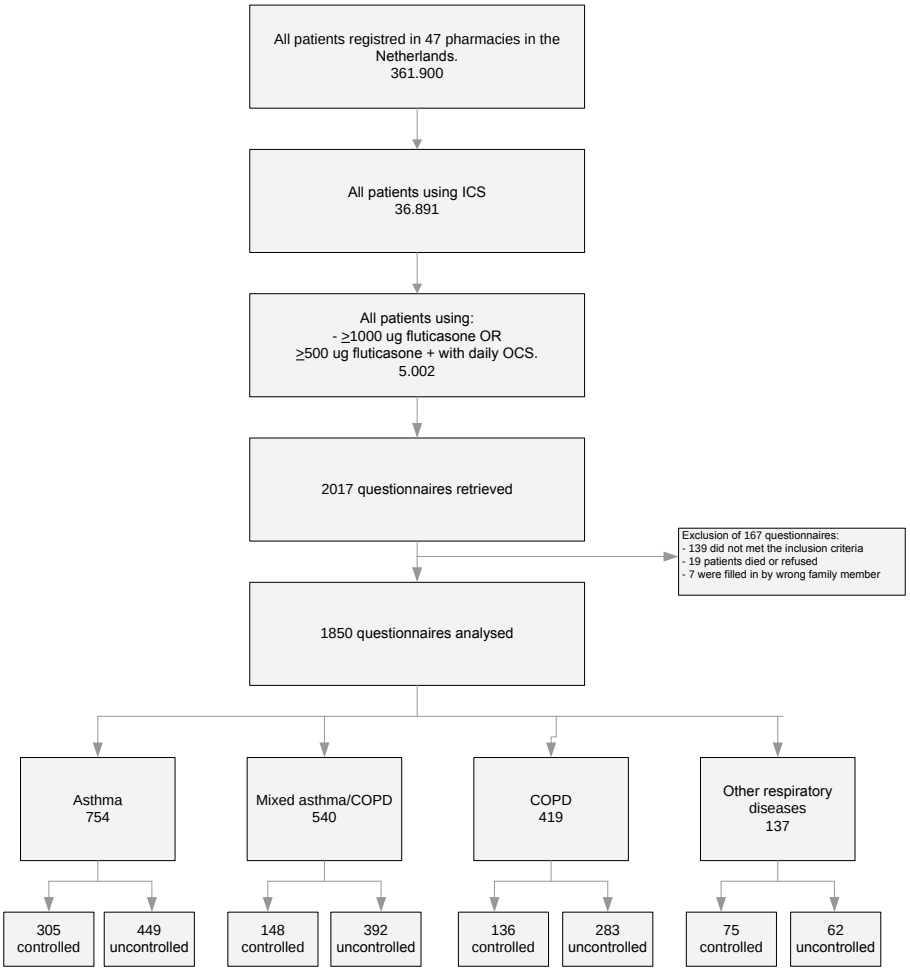

Figure 1 | Trial Diagram

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).

Table 1 | Characteristics of patients with asthma, mixed asthma, COPD or other respiratory disease

	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 (600-1000)	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

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).

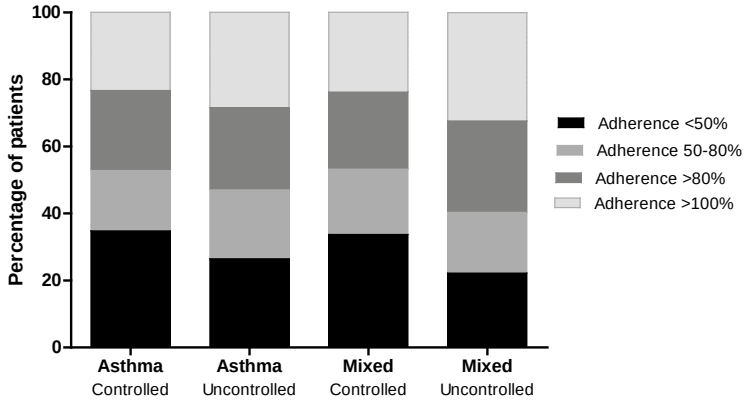

Figure 2 | Adherence in patients with controlled vs uncontrolled asthma

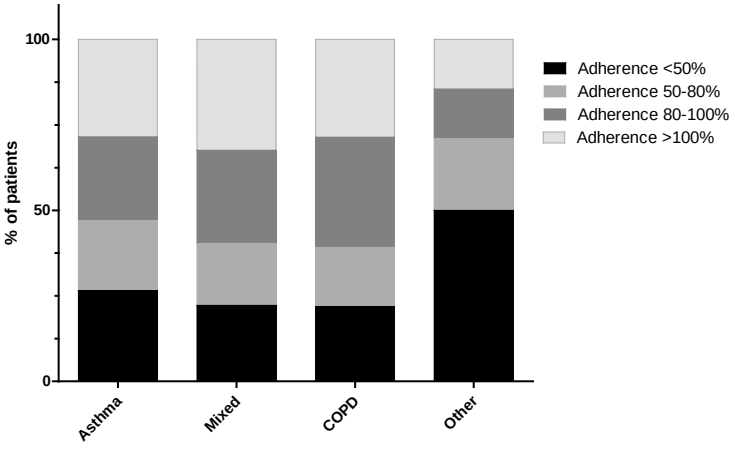

Figure 3 | Adherence in patients with asthma, mixed asthma/COPD, COPD and other respiratory diseases

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 with 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
Adherence				
- <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 traits [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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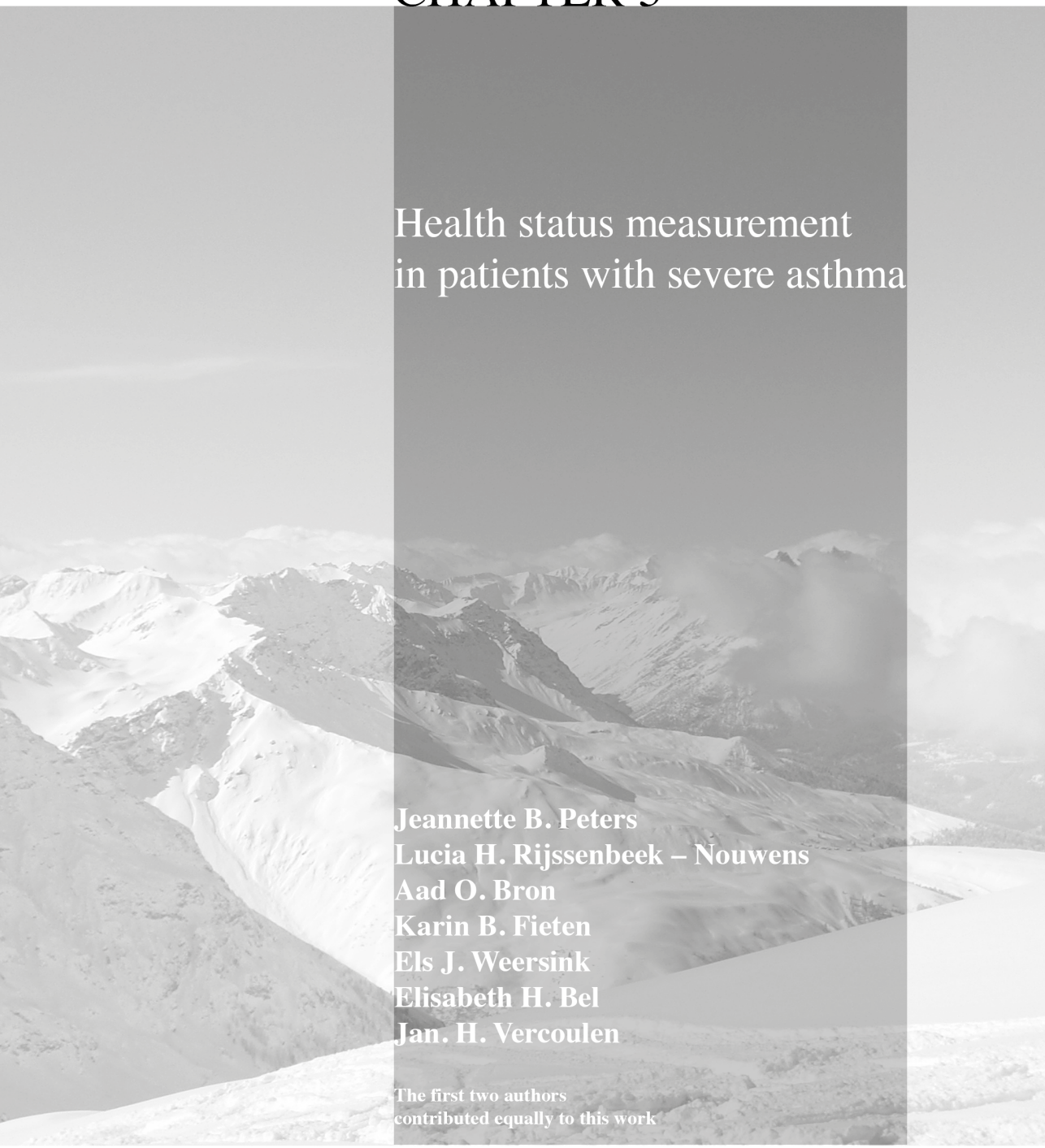
CHAPTER 3



Health status measurement in patients with severe asthma

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Abstract

Background

Patients with severe asthma experience problems in different areas of their health status. Identification of these areas will provide insight in the patients needs and perhaps in what makes the asthma more severe. Current asthma questionnaires measure only few aspects of health status, and lack information about the clinical relevance of the score for the individual patient. The Nijmegen Clinical Screening Instrument (NCSI) was recently developed for use in clinical practice and provides a detailed picture of the patients' symptoms, functional impairment, and quality of life.

Aim

Main purpose of this study is to evaluate the use of the NCSI as compared to the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) in measuring the impaired areas of health status in patients with severe asthma.

Methods

The Nijmegen Clinical Screening Instrument (NCSI), Asthma Quality of Life Questionnaire (AQLQ), and Asthma Control Questionnaire (ACQ) were measured in 167 patients with severe asthma. Pearson correlations were calculated between sub-domains of the NCSI and subscales of the AQLQ and ACQ.

Results

The NCSI measures more aspects of health status as compared to the ACQ and AQLQ in patients with severe asthma. Beside symptoms, subjective impairment, and emotions the NCSI also measures general Quality of Life, satisfaction with physical functioning, satisfaction with relations, fatigue, and behavioral impairment. On all sub-domains of the NCSI proportions of patients with normal, mild and severe problems were found. Heterogeneity was found on the number and on the combination of sub-domains on which patients reported severe problems.

Conclusions & Clinical relevance

The NCSI provides a more detailed picture of the individual patient with severe asthma than the ACQ and AQLQ. The use of the NCSI might allow quick identification of the problem areas and possible factors that impair health status.

Introduction

Patients with severe asthma suffer from serious problems in health status, such as symptoms during day- and nighttime[1], impairments in daily life activities[2], and lower quality of life (QoL)[3-6]. For adequate assessment and management of patients with severe asthma a detailed evaluation of patients' needs would be helpful to identify the factors that influence their health status. An instrument that provides a detailed picture of the different aspects of the patient's health status would be very useful. This information would guide treatment, help to open up the communication with the patient, and to improve the patient's self-management.

Many disease specific and generic questionnaires exist that measure aspects of health status. In asthma the Asthma control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) and to a lesser extend the St George Respiratory Questionnaire (SGRQ) and Quality of Life for Respiratory Illness Questionnaire (QoL-RiQ) are used for this purpose[7-10]. These instruments, especially the AQLQ and ACQ, are widely used in research, have proven to be valid, reliable, and are able to measure change, to describe groups and effects of interventions. However, on the level of the individual patient and in clinical care these instruments seem less appropriate. The ACQ only indicates whether the asthma is controlled or uncontrolled in a patient and provides no information on health status. The AQLQ measures only four domains, and lacks normative data, which means that the clinical relevance of particular scores on the level of the individual patient is unclear.

The Nijmegen Clinical Screening Instrument (NCSI) was specifically developed for use in clinical care of patients with COPD, to detect the problems in health status on individual patient base[11]. The NCSI measures eleven sub-domains of health status covering aspects of physiological functioning, symptoms, functional impairment and Quality of life with a battery of subscales from disease specific and generic questionnaires, as well as the results of lung function test. For each sub-domain of the NCSI normative data indicating normal functioning, mild problems and severe problems were collected. Immediately after the patient has completed the questionnaire part on the computer, are the results presented on the graphical PatientProfileChart (Figure 1) [11].

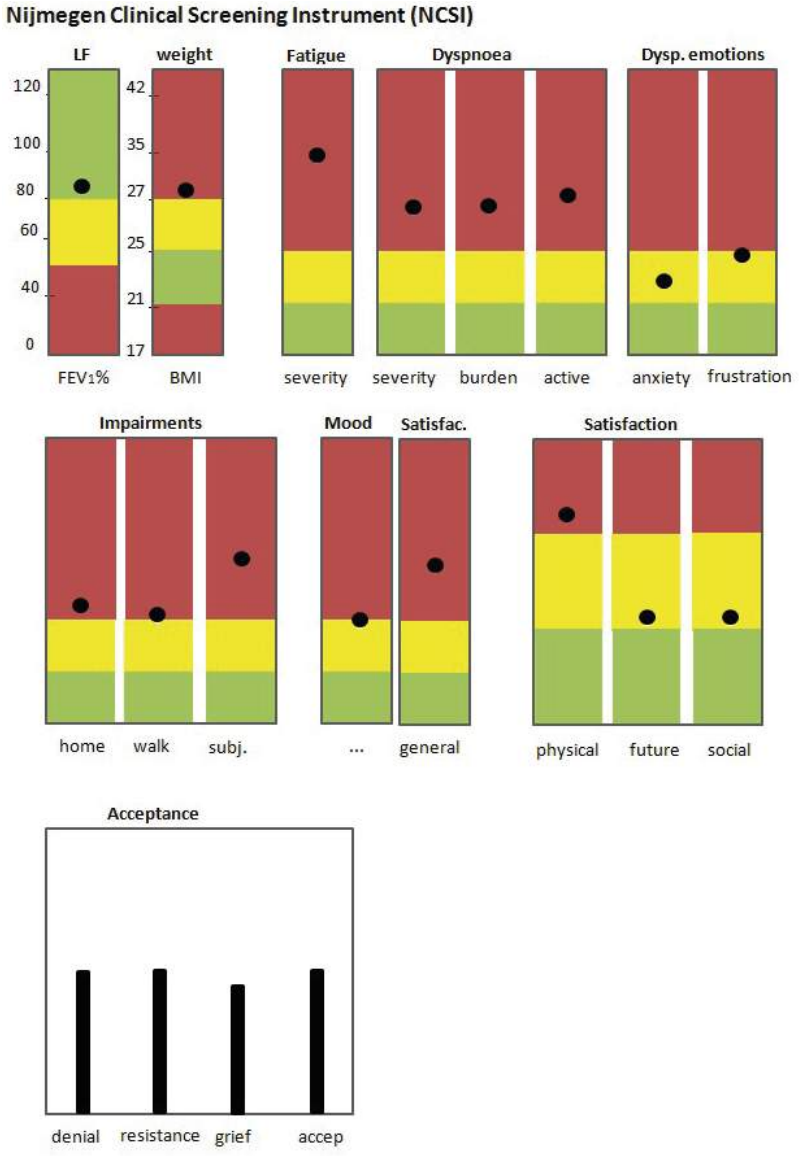

Figure 1 | The PatientProfileChart: a graphical representation of the patient's scores on the diverse aspects of health status as measured by the NCSI.

Note: In this figure we plotted the mean score of the study group (black dots) on that particular aspect instead of the individual score which is normally plotted in the graphs. The green area represents normal functioning, yellow area mild problems, and red area severe problems.

Although developed and validated in patients with COPD[11], have previous studies shown that all NCSI sub-domains are relevant in other diseases as well, including Q-fever[12, 13], and cardiac diseases (submitted). We hypothesized that the NCSI can be used also in patients with asthma.

Asthma and COPD have overlapping clinical characteristics and both patient groups report similar problems in health status. Moreover, patients with severe asthma are known to experience severe symptoms, functional impairment, and lower QoL[1-6]. Therefore, a group of patients with severe asthma would be most suitable to examine whether the NCSI can identify problems in health status in patients with severe asthma.

The main purpose of this study is to evaluate the NCSI in measuring the unmet needs in patients with severe asthma. The primary aim is to evaluate the internal consistency of the NCSI, and to investigate the relationships between the sub-domains of the NCSI, the ACQ total, and the AQLQ domains in patients with severe asthma. The secondary aim is to evaluate to what extent the NCSI measures other sub-domains of health status as compared to the disease specific AQLQ and ACQ, and whether these sub-domains are relevant in patients with severe asthma.

Methods

Study design

This cross-sectional study was conducted in patients with severe asthma who were referred to the Dutch Asthma Centre in Davos for high altitude treatment. On admission, all patients were assessed according to a systematic protocol. The study was approved by the Medical Ethical Committee of the Amsterdam Medical Centre and the approval was adopted by the Asthma Centre Davos. Written informed consent was obtained from all patients participating in the study. All data was collected in usual care, shortly after admission, and anonymized before analysis.

Study population

Adult patient (18-75 years) with a diagnosis of severe asthma who were referred to the Dutch Asthma Centre Davos, Switzerland, between January 2008 and January 2010 were asked to participate in the study. Severe asthma was defined according to the international criteria[14]. Dutch lung physicians send patients with severe asthma to the high altitude clinic in Davos, when optimal treatment, according to the GINA guidelines at sea level is not enough to reach control of asthma[15]. All patients were prescribed high doses of inhaled corticosteroids ($\geq$ 1000µg·day of fluticasone or equivalent) or oral corticosteroids, combined with long-acting bronchodilators for at least 1 year, in accordance to the GINA Guidelines stages 4-6 [15]. Most patients also used additional asthma medications (e.g. antihistamines, montelukast. Theophylline etc.). Patients with a smoking history >15 years, had to show reversibility in FEV_1 to short-acting beta agonist >12 % predicted in order to exclude patients with smoking related COPD. All patients were symptomatic and had experienced at least one severe exacerbation during the past year requiring a course of oral corticosteroids. Before referral to the high altitude clinic, inhalation technique and adherence with treatment was checked by the referring pulmonologist.

Questionnaires

AQLQ. The Asthma Quality of Life Questionnaire standardized version (AQLQ-S) [8] measures four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Scores range from 1 to 7, lower scores indicate more problems.

ACQ. The Asthma Control Questionnaire (ACQ)[7, 16] consists of six items which are scored from 0 (totally controlled) to 6 (severely uncontrolled) covering day and nighttime symptoms, activity limitations and rescue bronchodilator use. The cut-off point for well-controlled asthma is lower than 1.5 [7].

NCSI. The Nijmegen Clinical Screening Instrument (NCSI) [11] is a battery of existing tests and disease specific and generic instruments that provide a detailed assessment of health

status. The NCSI covers four main domains: physiological functioning, symptoms, functional impairment, and quality of life. These main domains are subdivided into eleven sub-domains that measure: airflow, body composition, static lung volumes (excluded in the present study), subjective symptoms, dyspnea emotions, fatigue, behavioral impairment, subjective impairment, general QoL, health related QoL, and satisfaction relations. See Table 1 for the definitions of the sub-domains and the included tests and instruments by which these sub-domains are measured [10, 17-22]. Completion of the questionnaire part of the NCSI is computerized and scoring is automated [22]. Normative data for each subscale were collected in healthy subjects and different samples of patients with COPD to identify cut-offs scores indicating normal functioning, mild problems or severe problems[11]. For each patient a personal profile can be made visible on the PatientProfileChart, see Figure 1. For all sub-domains: the higher the score the more problematic.

Measures

Lung function parameters. Forced expiratory volume in 1 second (FEV_1) was assessed after maintenance medication and inhalation of 400 µg salbutamol. Exhaled nitric oxide measurements were performed by standardized method using the NIOX [23].

Sensitisation to specific IgE was assessed with a panel of common aero-allergens (house dust mite, mixed grass and birch pollen, cat and dog dander and Aspergillus) by UniCap and expressed in kU/L. Patients were classified as allergic sensitized if IgE to one or more allergens was > 0.35 kU/l.

Statistics

Data are presented as mean ± standard deviation (SD), unless stated otherwise. Cronbach's Alpha reliability coefficients were calculated to study the internal consistency reliability of the items of each sub-domain/subscale of the NCSI, ACQ and AQLQ, an $\alpha > 0.70$ is considered reliable. Pearson correlation coefficients were calculated to study the relationships between the sub-domains of the NCSI, the ACQ total, and the subscales of the AQLQ. Conceptual similarity was defined by a correlation of 0.70 or higher. To avoid Type I error due to multiple testing P was set at 0.01. All statistics were performed by using SPSS 16.0 (SPSS Inc, Chicago, IL.).

Table 1 | Domains, sub-domains, definitions, instruments and number of included items from the instrument of the questionnaire part of the Nijmegen Clinical Screening Instrument (NCSI).

Domain	sub-domain	Definition	Instruments/measurement	No of items
Physiological functioning	Airflow		Post bronchodilator FEV_1% predicted	
	Body composition		Body Mass Index	
Symptoms	Subjective symptoms	The patient's overall burden of pulmonary symptoms	PARS-D Global Dyspnea Activity [20] PARS-D Global Dyspnea Burden [20]	2
	Dyspnoea emotions	The level of frustration and anxiety a person experiences when dyspnoeic	DEQ Frustration [20] DEQ Anxiety [20]	6
	Fatigue	The level of experienced fatigue	CIS Subjective fatigue [21]	8
Functional impairment	Behavioural impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP Home Management [22] SIP Ambulation [22]	22
	Subjective impairment	The experienced degree of impairment in general	QoLRiQ General Activities [10]	4
Quality of life	General Quality of Life	Mood and the satisfaction of a person with his/her life as a whole	BDI Primary Care [17] Satisfaction With Life Scale [19]	12
	Health-related Quality of Life	Satisfaction related to physical functioning and the future	Satisfaction physiological functioning [20] Satisfaction future [20]	2
	Satisfaction relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction spouse [20] Satisfaction social [20]	2

PARS-D: Physical Activity Rating Scale-Dyspnea; DEQ: Dyspnea Emotions Questionnaire; CIS: Checklist Individual Strength; SIP: Sickness Impact Profile; QoLRiQ: Quality of Life for Respiratory Illness Questionnaire; BDI, Beck Depression Inventory

Results

Subject characteristics

One hundred and eighty patients were admitted to the high altitude clinic between January 2008 and January 2010, of which 167 agreed to participate in the study. Thirteen patients were not able to fill the questionnaires adequately because of illiteracy or did not agree to participate for personal reasons. The baseline characteristics of the 167 patients with severe asthma included in this study are presented in Table 2. Uncontrolled asthma was found in 91% (ACQ >1.5) of the patients in this study.

Table 2 | Patient characteristics (N = 167) Data are presented as *N* (%), mean ± SD or median (range), unless otherwise stated.

Age (yrs)	44.5 ± 15
Sex (male) N (%)	58 (35%)
Asthma duration (yrs)	30 (1-66)
Sensitized to allergens	112 (67%)
BMI	28.1 (range 16.8-54.5)
Ex-smokers	57 (34%)
FEV_1% pred.	87.7 ± 24.5
FeNO ppb	20.7 (4-233)
ACQ score	3.2 ± 1.1
ICS µg/day	0-8000
Daily OCS N (%)	82 (49%)

BMI: body mass index; FEV1: forced expiratory volume in 1 s; % pred: % predicted; FeNO: exhaled nitric oxide fraction; ACQ: Asthma Control Questionnaire score, 0-6, where 0 = well controlled; ICS: inhalation corticosteroids; OCS: oral corticosteroids.

NCSI-scores in severe asthma patients

Overall, high percentages of severe problems were found in the sub-domains of symptoms, functional impairment, and QoL (Figure 2). The most prevalent sub-domains with severe impairment were subjective symptoms (82.0%), fatigue (90.4%), subjective impairment (86.8%), and general QoL (81.4%). Furthermore, 31.7% of the patients had clinically relevant depressive symptoms (subscale within sub-domain general QoL, not shown).

Diversity between patients was found in the number of sub-domains with severe problems (Figure 3). Nineteen percent of patients were severely impaired in all eight sub-domains of the NCSI, and 80% of patients had five or more severely impaired sub-domains.

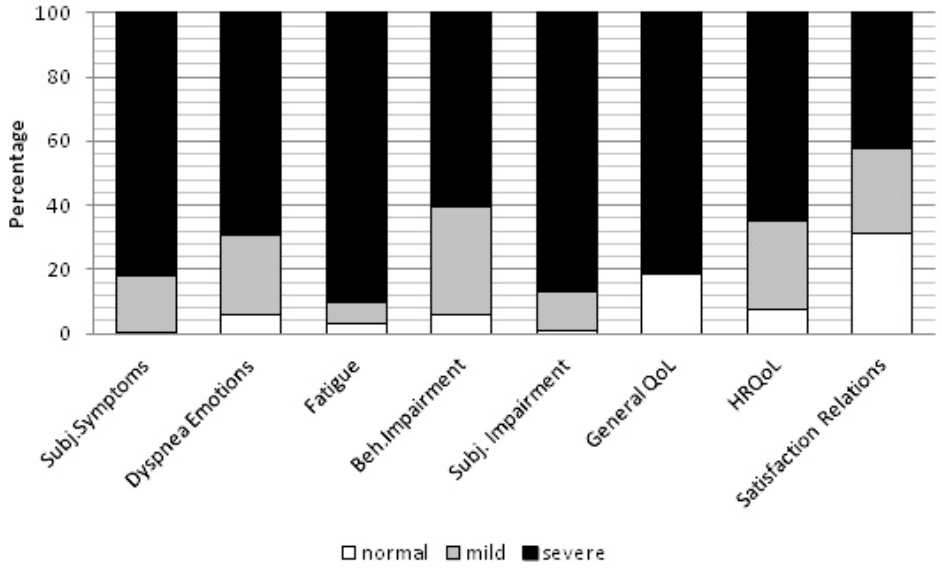

Figure 2 | Percentages of patients with asthma with normal functioning, mild problems and severe problems for each sub-domain of the NCSI

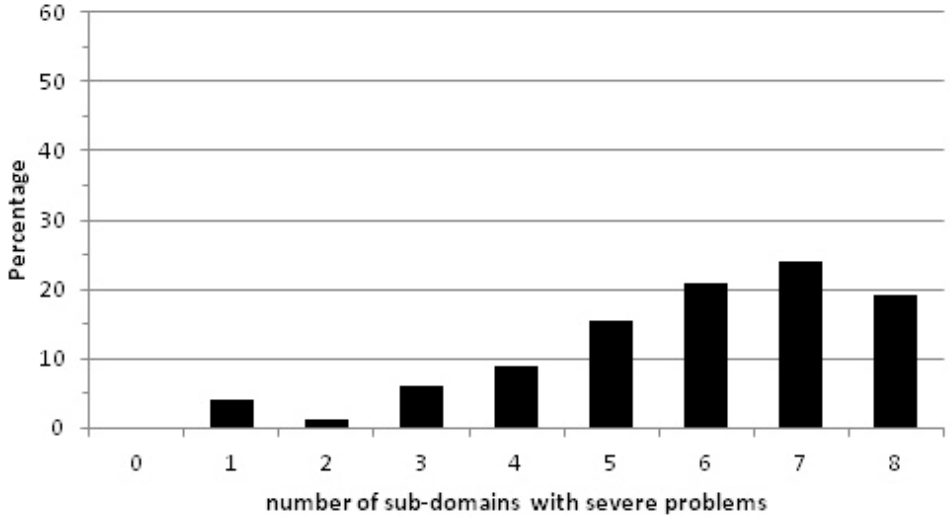

Figure 3 | Distribution of percentages of patients with severe asthma with severe problems on *n* number of sub-domains of the NCSI

Inter correlations of the questionnaires

With respect to the AQLQ-S, the domain activity reached conceptual similarity with the domain symptoms and environmental stimuli, although the latter two domains were only moderately related (Table 3).

Correlations between most of the NCSI sub-domains were moderate to absent, as shown in Table 4. Only the sub-domains subjective symptoms and subjective impairment reached the criterion for conceptual similarity (r > 0.70), indicating that these two sub-domains measure highly related concepts.

Table 3 | Correlations between the subscales of the Asthma Control Questionnaire (ACQ) and domains of the Asthma Quality of Life Questionnaire (AQLQ).

		ACQ total	AQLQ Symptoms	AQLQ Activity limitation	AQLQ Emotional function	AQLQ Environmental stimuli	AQLQ total
ACQ	total	1.00					
AQLQ	symptoms	**-0.83**	1.00				
AQLQ	activity limitations	-0.67	**0.85**	1.00			
AQLQ	emotional stimuli	-0.35	0.54	0.39	1.00		
AQLQ	environmental stimuli	-0.35	0.48	0.69	0.34	1.00	
AQLQ	total	**-0.74**	**0.90**	**0.91**	0.64	**0.73**	1.00

Note. N = 167. Correlations > 0.70 in **bold**.

Reliability of the questionnaires

For all sub-domains the internal consistency was good, irrespective of the questionnaire used, except for the NCSI sub-domains of QoL see Table 5. However, the Cronbach's alpha of the two separate subscales that together measure general QoL was good (Satisfaction With Life Scale (SWLS) 0.88 and Beck's Depression Inventory (BDI) 0.83, respectively.

Table 4 | Correlations between the sub-domains of the Nijmegen Clinical Screening Instrument (NCSI).

NCSI main domain		Symptoms			Functional impairment		Quality of Life		
	Sub-domain	subjective symptoms	dyspnea emotions	Fatigue	subjective impairment	behavioral impairment #	general QoL	health related QoL	satisfaction relations
Physiological	FEV_1% of predicted	-0.23	-0.13 ns	0.04 ns	-0.19ns	-0.19 ns	-0.05ns	-0.07 ns	-0.14ns
functioning	FeNO	0.09 ns	0.18 ns	-0.15 ns	0.06 ns	-0.09 ns	0.14 ns	0.04 ns	-0.01ns
	BMI	0.23	0.05 ns	0.01 ns	0.23	0.23 ns	0.03 ns	0.17 ns	0.01ns
Symptoms	subjective symptoms	1.00							
	dyspnea emotions	0.35	1.00						
	fatigue	0.37	0.09 ns	1.00					
Functional	subjective impairment	0.71	0.25	0.46	1.00				
impairment	behavioral impairment#	0.34 ns	0.18 ns	0.32 ns	0.34	1.00			
Quality of Life	General QoL	0.24	0.67	0.20 ns	0.23	0.34 ns	1.00		
	health related QoL	0.47	0.43	0.41	0.54	0.43	0.67	1.00	
	satisfaction relations	0.17 ns	0.29	0.09 ns	0.20 ns	0.26 ns	0.52	0.45	1.00

Note. N=167 except for behavioural impairment due to a technical error (N=53).

Conceptual similarity between the questionnaires

The ACQ-total score reached conceptual similarity with AQLQ-symptoms and nearly with AQLQ-activity limitations (Table 6). The ACQ-total showed conceptual similarity only with NCSI subjective impairment, and nearly with NCSI subjective symptoms.

The AQLQ-symptoms showed conceptual similarity with NCSI subjective impairment, and nearly with NCSI subjective symptoms. AQLQ-activity limitations nearly reached conceptual similarity with NCSI subjective impairment. AQLQ-emotional functioning reached conceptual similarity with NCSI dyspnea emotions. AQLQ-environmental stimuli did not reach conceptual similarity with any NCSI sub-domain.

Nor the ACQ or domains of the AQLQ did show conceptual similarity with the NCSI sub-domains fatigue, behavioral impairment, general QoL, health-related Qol, and satisfaction with relations. The NCSI, ACQ, and AQOLQ were not significantly related to FEV_1, F_{eNO}, BMI.

Table 5 | Cronbach's reliability coefficient (α), score range, mean (SD) and 95% confidence interval of the three questionnaires, the Asthma Control Questionnaire (ACQ), the Asthma Quality of Life Questionnaire (AQLQ) and the Nijmegen Clinical Screening Instrument (NCSI) in patients with severe asthma (N = 167).

	Cronbach's Alpha	Score range	Mean ± SD	95% CI
ACQ total	0.87	0-6	3.2 ± 1.1	2.9 - 3.3
AQLQ				
symptoms	0.88	1-7*	3.9 ± 1.1	3.7 – 4.1
activity limitation	0.88	1-7*	3.5 ± 1.2	3.3 – 3.6
emotional function	0.84	1-7*	4.9 ± 1.3	4.7 – 5.1
environmental stimuli	0.77	1-7*	4.2 ± 1.5	4.0 – 4.5
total		1-7*	4.0 ± 1.0	3.8 – 4.1
NCSI-Symptoms				
subjective symptoms	0.89	2-20	14.1 ± 4.2	13.5 – 14.8
dyspnea emotions	0.83	6-24	12.0 ± 4.0	11.4 – 12.6
fatigue	0.82	8-56	47.1 ±8.7	45.8 – 48.5
NCSI-Functional impairment				
behavioral impairment #	0.79	0-99.2	26.2 ± 20.5	20.5 – 31.8
subjective impairment	0.89	4-28	17.7 ± 5.4	16.9 – 18.5
NCSI- Quality of life				
general QoL	0.54	1-101.6	28.0 ± 17.8	25.3 – 30.7
health related QoL	0.47	2-10	6.1 ± 1.7	5.8 – 6.3
satisfaction relations	0.62	2-10	4.1 ± 2.0	3.8 – 4.4

Note. Pearson correlations between the sub-domains of the NCSI , the ACQ, and the AQLQ for patients with asthma at start of rehabilitation. N = 167 except for behavioural impairment due to technical error (N = 53). * Lower scores indicate more problems

Table 6 | Correlations between the sub-domains of the Nijmegen Clinical Screening Instrument (NCSI), the Asthma Control Questionnaire (ACQ), and the Asthma Quality of Life Questionnaire (AQLQ) to examine conceptual similarity.

	ACQ total	**AQLQ Symptoms**	**AQLQ Activity limitation**	**AQLQ Emotional function**	**AQLQ Environmental stimuli**	**AQLQ total**
Physiological functioning						
FEV_1% predicted	-0.26	0.16 ns	0.09 ns	0.20 ns	0.01 ns	0.14 ns
FeNO	0.12 ns	-0.07 ns	0.05 ns	-0.12 ns	0.19 ns	0.01 ns
BMI	0.18 ns	-0.12 ns	-0.16 ns	-0.07 ns	-0.02 ns	-0.13 ns
NCSI symptoms						
subjective symptoms	***0.66***	***-0.67***	-0.58	-0.40	-0.29	-0.64
dyspnea emotions	0.21	-0.30	-0.16 ns	***-0.69***	-0.16 ns	-0.36
fatigue	0.44	-0.47	-0.43	-0.16 ns	-0.19 ns	-0.43
NCSI functional impairment						
behavioral impairment#	0.49	-0.53	-0.59	-0.41	-0.39	-0.60
subjective impairment	**0.77**	**-0.70**	***-0.65***	-0.37	-0.30	***-0.68***
NCSI Quality of Life						
general QoL	0.18 ns	-0.29	-0.21	-0.54	-0.23	-0.36
health related QoL	0.40	-0.46	-0.42	-0.50	-0.24	-0.50
satisfaction relations	0.15 ns	-0.18 ns	-0.25	-0.31	-0.23	-0.27

Note. Pearson correlations between the sub-domains of t the Nijmegen Clinical screening Instrument (NCSI), the Asthma Control Questionnaire (ACQ), and the Asthma Quality of Life Questionnaire (AQLQ) for patients with difficult to control asthma at start of rehabilitation. N = 167 except for behavioural impairment due to technical error (N = 53). Correlations > 0.70 in **bold**. Ns = not significant. Correlations in 'bold-italic' reach conceptual similarity

Discussion

The present study shows that the Nijmegen Clinical Screening Instrument (NCSI) measures more aspects of health status than the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ-S) in patients with severe asthma. All sub-domains of the NCSI proved to be relevant in this patient group.

The main aim of this study was to evaluate the added value of the NCSI to measure aspects of health status above the frequently used disease specific instruments AQLQ and ACQ. The AQLQ and the ACQ are used in numerous studies to evaluate interventions [24-27] and to describe groups of patients with asthma [28]. These studies have provided important information about the experienced symptoms, activity limitations, emotional functioning, and impact of environmental stimuli on these patients. However, health status most certainly comprises of more sub-domains than the four subscales covered by the AQLQ and the one subscale of the ACQ. We expected that the ten sub-domains of the NCSI probably measure the same, but certainly even more, aspects of health status than the AQLQ.

Both the AQLQ and the NCSI measure the subjective symptoms, subjective impairment, and emotions. However, the NCSI measures also airflow, body composition and items that measure the experienced fatigue, satisfaction with life in general, mood, satisfaction with relationships and future, and sickness-related behavioral impairment that are not covered by the AQLQ and ACQ. On all eight NCSI sub-domains, measured by the questionnaire part, high proportions of patients with serious problems were found. In addition, all eight sub-domains were shown to represent conceptually distinct aspects of the patient health status, as evidenced by the low intercorrelations. Only the sub-domains subjective symptoms and subjective impairment showed conceptual similarity. The domain AQLQ activity limitation showed high intercorrelations with the domains symptoms and environmental stimuli indicating that they measure similar concepts. However, the moderate correlation between symptoms and environmental stimuli indicate that these two domains measure separate concepts, thus both share different parts with the domain activity limitation. This is not surprising since the items of activity limitation measure activity limitation due to environmental stimuli and due to their asthma symptoms. Thus, the NCSI questionnaire part measures seven aspects of health status whereas the AQLQ measures three distinct aspects of health status.

This suggests that, in patients with severe asthma, the NCSI is capable of providing a more complete picture of the patient's problems and needs on health status as compared to the ACQ and AQLQ.

The present study shows that all NCSI subscales represent highly relevant sub-domains of health status in patients with severe asthma. In addition, heterogeneity was found between patients with respect to the number of sub-domains and in the combination of sub-domains on which patients experienced severe problems. Low to absent correlations were not only found between the non-physiological sub-domains of the NCSI, but also between physiological functioning and symptoms, behavioral impairment, and QoL. This is not a new phenomena, Haldar et al[29] also found that symptom perception is not always in concordance with eosinophilic airway inflammation, and concluded that both, symptoms and physiologic parameters, have to be measured to get a complete picture.

Several limitations of the present study should be kept in mind with respect to the generalizability of the results. In this study we included a select group of patients, more specifically patients with severe asthma referred to a high-altitude inpatient pulmonary clinic. Even in this highly selected group of patients with severe asthma, marked heterogeneity was found. Which makes it feasible that this might even be more pronounced in a more general sample of patients with asthma. The moderate internal consistencies of the sub-domains of QoL are another limitation. In COPD the same problem exists, a possible explanation is that the included subscales measure different concepts, however further refinement will be necessary. One might question the adequacy of the cut-off scores for normal functioning on the sub-domains of the NCSI. Since, these cut-offs were based on a group of healthy persons matched by age and sex to a COPD study group[11]. This could lead to an underestimation of problems in patients with asthma, because asthma patients are generally somewhat younger. Morroy et al [13], found no significant differences between patients with Q-fever older and patients with Q-fever younger than 50 years on seven of eight NCSI sub-domains, patients younger than 50 years had significant higher scores on dyspnea emotions.

The reason for this study was the need for an instrument that would enable a detailed evaluation of the needs of patients with severe asthma and that could help to identify the factors that aggravate, complicate, or influence disease perception. The NCSI provides a detailed assessment of health status, and includes normative data, which render the patient's scores on each sub-domain clinically meaningful[11].

The powerful mechanism is not the NCSI as instrument per sé, but by discussing the PatientProfileChart with the patient. The PatientProfileChart visualizes on which sub-domain a patient functions normally and on which sub-domain a patient experience severe problems. The PatientProfileChart allows the doctor and other healthcare providers to quickly identify the factors leading to disease burden by discussing the results.[30] More-

over, the discussion with the patient also facilitates shared-decision making, which has proven to be important in promoting adherence.[31]. Moreover, the complexity of the balance between health status and the underlying problems and self-management capacities, may become visible in the discussion. This information may help in guiding non-pharmacological treatment since pharmacological treatment alone seems to be insufficient in patients with severe asthma.[31] In COPD this approach have been implemented in usual care since several years and has proven its clinical relevance. The next step would be to implement the NCSI in treatment of patients with severe asthma, and examine its sensitivity to change.

Conclusions

The present study showed that the NCSI, ACQ and AQLQ measure highly relevant aspects of health status in patients with severe asthma. However, the NCSI measures more aspects of health status that are not covered by the ACQ and AQLQ. The NCSI in combination with the PatientProfileChart might help to identify the impact on daily life, symptoms, QoL, and impairments in the individual patient with severe asthma.

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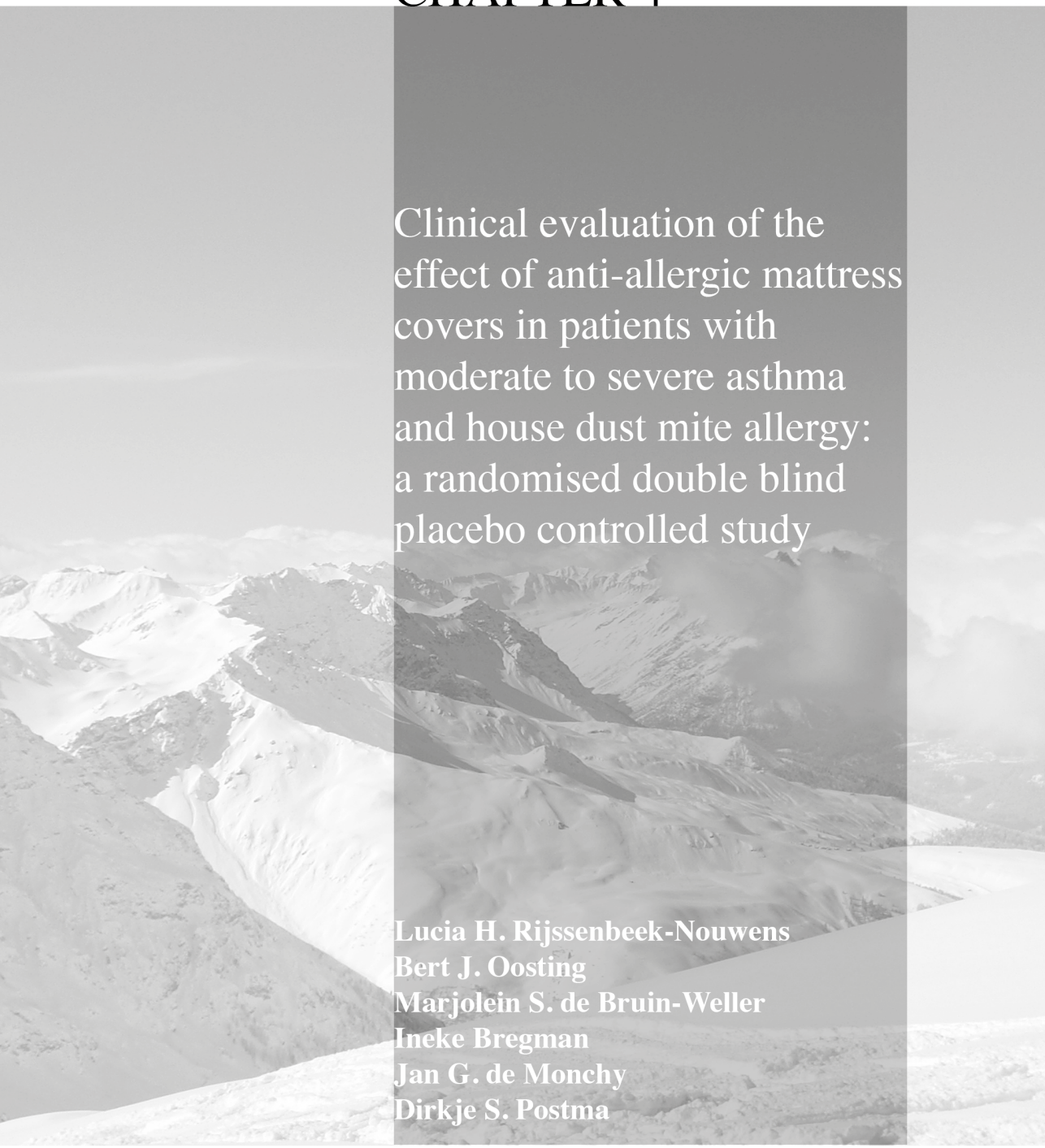
CHAPTER 4



Clinical evaluation of the effect of anti-allergic mattress covers in patients with moderate to severe asthma and house dust mite allergy: a randomised double blind placebo controlled study

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Abstract

Background

The use of anti-allergic mattress covers in patients with asthma can result in a large reduction in the level of house dust mite allergen in dust samples. Apart from a reduction in histamine induced bronchial hyperresponsiveness, there are few data on the effect of mattress covers on clinical efficacy and quality of life in patients with moderate to severe asthma.

Methods

Thirty patients with asthma and house dust mite allergy were studied in a randomised, double blind, placebo controlled study. Before and after using anti-allergic covers for 1 year, dust was collected from the mattresses to determine concentrations of Dermatophagoides pteronyssinus (Der p1), and bronchial hyperresponsiveness and quality of life were measured. The patients scored their symptoms (lungs and nose), morning and evening peak flow values, and rescue medication for 14 days before and after the intervention period.

Results

There was a significant reduction in the concentration of Der p 1 in the dust collected from the mattresses in the actively treated group after 1 year compared with before treatment; no change was found in the placebo group. In both the actively treated and placebo groups there was no significant improvement in PC20 histamine. Quality of life improved similarly in both groups. The symptom score of the lower airways did not significantly change in either group. A significant decrease in nasal symptom score was seen in the actively treated group compared with before treatment, but there was no significant difference between the groups. No changes in morning and evening peak flow values, peak flow variability, nor in the use of rescue medication were found in either group.

Conclusion

The use of anti-allergic mattress covers results in significant reductions in Der p 1 concentrations in carpet-free bedrooms. However, in patients with moderate to severe asthma, airways hyperresponsiveness and clinical parameters are not affected by this effective allergen avoidance.

Introduction

Exposure and sensitisation to house dust mite (HDM) allergens has been established as an important risk factor for the development of asthma in most parts of the world[1]. The rate of sensitisation to mite allergens is directly related to its exposure[2]. The severity of asthma is also related to allergen exposure[3], as measured by the level of bronchial hyperresponsiveness, forced expiratory volume in 1 second (FEV1), and variability in peak expiratory flow (PEF). The relation between exposure and asthma symptoms in sensitised patients is complex, but asthma is usually more severe in sensitised patients who are exposed to higher allergen levels[3]. In effectively mite allergen free environments such as hospitals [4] or high altitude Alpine sanatoria [5,6] the condition of asthma patients improves both symptomatically and in terms of non-specific bronchial responsiveness. These results suggest that avoidance of mite allergen leads to a decrease in airways inflammation with consequent improvement in bronchial hyperresponsiveness and symptoms. It may take many months for the clinical effects to become fully apparent and re-exposure often results in a rapid relapse[7]. It is therefore essential to achieve and maintain a major reduction in exposure.

Many methods of allergen avoidance have been tested in small intervention studies, but only a few have been subjected to controlled trials. Some show benefit when reduction in allergen exposure can be achieved [8,9]; others seem to be ineffective[10,11].

Reduction of allergen exposure in the bedroom is the primary target of avoidance measures, since the bed is the most important habitat and source of mite allergens to which we are exposed for many hours during nocturnal sleep. The most effective and probably most important avoidance measure is to cover the mattress, pillows, and duvets with mite allergen impermeable covers[8–10]. Acaricides have been shown to be ineffective[12], time and energy consuming, and they require repeated application. Carpets are also an important microhabitat for mite colonisation and a possible source from which beds can be reinfested[13], so this source of mites should also be eliminated. Allergen avoidance measures seem to be more effective in the early stage of the disease[14]. The effects of allergen avoidance measures in more advanced stages of asthma are not known.

A double blind, placebo controlled study was undertaken to investigate whether allergen impermeable covers as a single intervention are of clinical benefit to patients with moderate to severe asthma. Only non-smoking patients with a smooth bedroom floor whose disease had been stable for the previous 6 months were included. Patients with furry pets were admitted if they had no pet allergy. All had moderate to severe asthma and house dust mite allergy, severe bronchial hyperresponsiveness, and relevant exposure to house dust mite allergens. A study period of 1 year was chosen to exclude seasonal variation in exposure to Der p 1[15,16].

Methods

Patients

Thirty-eight patients aged 11- 44 years with a history of asthma and house dust mite allergy were recruited from the outpatients department of Asthmacenter Heideheuvel in Hilversum, The Netherlands, from January 1996 to December 1998. Informed consent was obtained from the patients or their parents. The patients were selected on the basis of increased bronchial responsiveness to histamine inhalation (PC20 < 4 mg/ml, 30 minute method), positive skin tests and/or raised specific IgE to house dust mite allergen, and relevant HDM exposure on the mattress (>1 µg Der p 1/g dust). All patients had FEV1 values >60% (predicted value). Patients had no history of respiratory tract infections in the previous 6 weeks or severe asthma attacks in the previous 6 months. None had received oral corticosteroids in the previous 6 months.

All patients gave informed consent. The medical ethics committee of Asthmacenter Heideheuvel approved the study.

Study design

The study was of a randomised, placebo controlled, double blind, parallel group design, comparing the effect of allergen impermeable encasings on the mattresses, pillows and bedcovers during 1 year with matching placebo encasings.

At the start of the study a trained respiratory nurse visited the patients to collect dust samples from the mattresses of the patients for Der p 1 measurement and to note the allergen avoidance measures already present in the house. All patients included in the study had smooth bedroom floors. Patients were instructed to wash their sheets each week at 60°C. Apart from the mattress encasings, no other allergen avoidance measures were taken. At the end of the study the same nurse visited the houses again to collect dust from the mattress covers.

The patients were included during the entire year; the inclusion period was 2 years. Pollen allergic patients were tested outside the pollen season.

At the first visit patients underwent clinical evaluation. FEV1 and vital capacity (VC) values were measured, skin tests performed, and a PC20 histamine was assessed. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate for 1 week before the bronchial histamine provocation test; theophyllines, oral β2 adrenergic agents, long acting inhaled β2 adrenergic agents, and antihistamines for 48 hours, and inhaled short acting β2 adrenergic drugs for 6 hours before the tests.

Collection and extraction of house dust

Before the intervention, at 4 and 8 months, and at the end of the intervention mattress dust was collected by the same vacuum cleaner (Philips Vitall 377, 1300 watt, Philips, Eindhoven, The Netherlands) from the whole mattress during 2 minutes with a special filter device (ALK, Horsholm, Denmark). At the start of the study dust was collected directly from the mattresses; at the end of the study dust was collected on top of the encasings. The filters were stored in the freezer at –20°C until analysis at the end of the study.

Der p 1 antigen was measured using enzyme linked immunosorbent assay (ELISA). Monoclonal antibodies against Der p 1 were immobilised on a 96-well plate. Incubation with the dust extracts was followed by a second incubation step with a polyclonal antibody (horseradish peroxidase, HRP). After adding 1,2-phenyldiamine HCl (OPD) as substrate, absorption at 490 nm was measured using an ELISA reader.

Histamine challenge

Histamine phosphate solutions (doubling concentrations from 0.25 to 32 mg/ml) were administered through a De Vilbiss 646 nebuliser with a gauged output of 0.13 mg/ml. The nebuliser was mounted on a valve box with an aerosol filter. The nebulisation time was 30 seconds, during which the patient was instructed to breath quietly. The test was started with inhalation of a phosphate buffer aerosol. Before inhalation three measurements of VC and FEV1 were performed (Jaeger Masterscreen). FEV1 was measured after each concentration. PC20 histamine was derived by linear interpolation.

Mattress encasings

Mattresses, pillows, and bedding in the intervention group were encased with covers supplied by Cara C'air (Allergy Control AC btm Velserbroek, Netherlands). The matched placebo covers were made by the same company. The encasings were placed in position by a research nurse and left in situ for 1 year.

Quality of life

Quality of life was assessed by the Quality of Life for Respiratory Illness Questionnaire (QoL-RIQ)[17]. The QoL-RIQ is a disease specific quality of life questionnaire for patients with asthma and COPD which consists of 55 items divided into seven domains: breathing problems (9 items), physical problems (9 items), emotions (9 items), situations triggering/enhancing breathing problems (7 items), general activities (4 items), daily and domestic activities (10 items), social activities, relationships and sexuality (7 items). To focus the questions on the patients' experiences, items are formulated in terms of "how much trouble" they had experienced from the mentioned symptom or emotion. In the case of activity related items, questions are stated in terms of "how much they were impeded" by their

disorder in carrying out that specific activity. Patients are asked to give their answer on a 70 point Likert scale ranging from "not at all" to "extremely" troubled or impeded. Reliability (test-retest, internal consistency) and validity have been proven[17].

Clinical parameters

During the 14 day period before the intervention and at the end of the 12 month intervention period the patients were asked to keep diary cards in which asthma and nasal symptoms, peak flow values, and medication use were recorded twice daily. Asthma symptoms included dyspnoea, cough, expectoration, and wheezing. Nasal symptoms included nasal blockage, rhinorrhoea, sneezing, and itching. Each item was scored on a scale from 0 (no symptoms) to 4 (severe symptoms).

The patients were trained in performing peak flow manoeuvres with the mini-Wright meter. They were instructed to perform three readings and to record the highest value in the morning when waking and in the evening before sleeping.

Patients were asked to continue their normal inhalation medication and to record extra rescue medication in case they needed it.

Data analysis

Statistical analyses were performed with SPSS. Comparisons within groups (before and after intervention) were made with the Wilcoxon signed rank test. Logarithmic data were analysed using the sign test. The Mann-Whitney U test was used for between group comparisons. p values of <0.05 were considered significant. Values are expressed as mean (SE) or as median (range).

Power calculations were performed. We expected a 20% increase in the PC20 histamine level. Based on the mean PC20 of the complete group of 1.59 (0.38) mg/ml, an increase to 1.91 (0.38) was expected. With a power of 99% of achieving a significant result at the 5% level, the calculated sample size was 29.3 patients. As 30 patients completed the study, a 20% change in PC20 histamine would have a probability of 99% of being noticed.

Results

Thirty-eight atopic non-smoking patients with asthma and house dust mite allergy entered the study. Eight patients did not finish the study, five from the placebo group and three from the treated group. In the placebo group three dropped out because of asthma instability, one because of moving to another city, and one because the recording of symptoms, peak flow and rescue medication was not sufficient to make an accurate analysis. In the treated group one individual dropped out because the study was too much of a burden, and two because of insufficient diary keeping. Drop out due to disease instability was significantly higher in the placebo group. 30 patients completed the entire study, 16 in the treated group and 14 in the placebo group (Figure1). The clinical characteristics of these patients are presented in Table 1. Although both groups had severe hyperresponsiveness (geometric mean values of PC20 histamine 1.75 and 1.27 mg/ml in the placebo and treated groups, respectively), three patients in each group did not regularly use inhaled steroids. The demographic characteristics of the two treatment groups were similar (Table 1). There were no significant differences between the two groups in PC20 histamine, FEV1, PEF, and medication used.

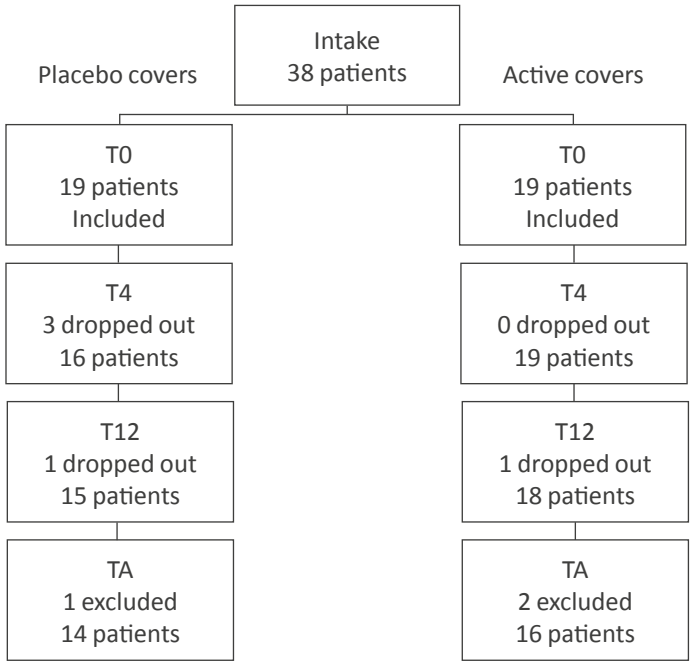

Figure 1 | Trial diagram: T0= baseline, T4= 4 months, T12= 12 months, TA= analysis

Table 1 | Clinical characteristics of study patients.

Patient	Age	Sex	FEV_1 (% pred)	PC_{20} hist (mg/ml)	Skin test*	Rhinitis	Medication asthma	Medication rhinitis
1	21	M	97	1,76	2,1	–	B, SB	–
2	11	M	79	0,74	1,1	+	B, SB	–
3	11	M	97	4	1,4	+	B, SB	–
4	29	M	81	0,33	1,2	–	F, SM	–
5	21	M	73	2,43	2	+	B, SB	B
6	27	F	70	0,9	1,2	+	B, SB	B
7	44	M	70	1,89	1,2	+	F, SM	F
8	17	F	138	1,78	1,9	+	–	B
9	40	M	64	1,13	1,6	+	B, SB	–
10	29	M	103	0,71	1,5	+	–	–
11	28	F	73	0,45	2,2	–	F, SB	–
12	12	M	106	4	1,6	+	B, SB	–
13	25	F	98	1,53	1,5	+	SB	–
14	30	M	100	2,9	1,5	–	B, SB	–
Mean	25		89	1,75	1,6			
SD	10		20	1,21	0,4			
Active group								
1	25	F	99	1,19	1,5	+	B, SB	–
2	29	M	99	0,95	1,6	–	B	–
3	41	M	67	3,79	2,2	+	B, SB	–
4	24	F	86	2	1,8	+	B, SB	–
5	31	M	81	1,22	1,5	–	–	–
6	24	M	80	0,55	1,1	+	B, SB	B
7	22	F	104	2,67	1,4	+	B	–
8	51	F	70	0,45	1,2	+	B, SB	B
9	32	M	68	0,42	1,1	–	B, SM	–
10	36	F	103	0,35	1,8	+	SB	B
11	42	M	75	0,42	1,2	–	B, SM	–
12	18	F	103	2,35	1,2	+	F, SM	F
13	40	F	98	0,86	1,6	+	B, SB	B
14	30	F	107	1,16	1,9	+	F, SB	F
15	41	F	97	0,98	1,1	–	B, SM	–
16	37	M	76	0,91	1,3	–	SB	–
Mean	33		88	1,27	1,5			
SD	9		14	0,97	0,3			

*X times histamine reaction.

B=beclomethasone or budesonide; F=fluticasone; SB=salbutamol; SM=salmeterol; FO=formeterol.

Der p 1 concentrations on mattresses

Figure 2 shows mean log Der p 1 concentrations on the mattresses before and 12 months after the start of the study in both groups. In the treated group Der p 1 concentrations on the mattresses were significantly lower after 1 year (26.19 (8.58) v 2.79 (0.88) µg/g fine dust, p=0.004). In the placebo group there was no significant reduction in Der p 1 (23.28 (10.44) v 25.11 (11.98) µg/g fine dust, p=0.18). A significant difference in the treatment induced change in Der p 1 concentration was seen between the two groups (p=0.04). The significant reduction in the Der p 1 concentration was present after 4 months and persisted throughout the year.

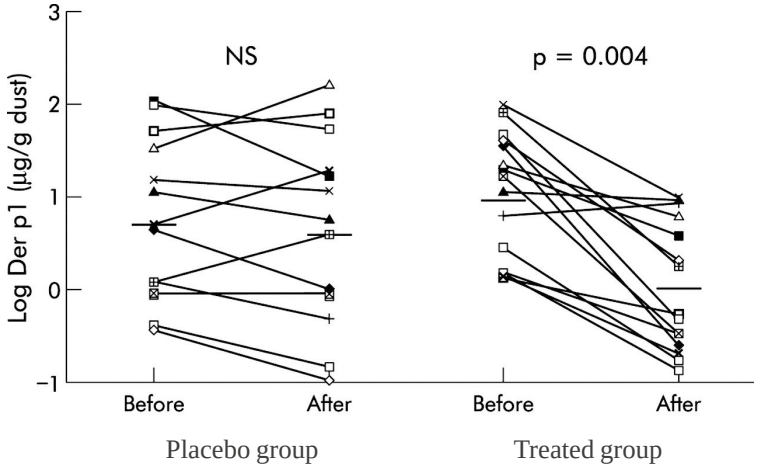

Figure 2 | Log values of mean Der p 1 levels (µg/g dust) before and after 1 year of intervention (treated: 0.97 v 0.03; placebo: 0.73 v 0.61).

Histamine challenge

At the start of the study the mean PC20 histamine was 1.45 (0.44) mg/ml and after 1 year this had risen to 1.66 (0.35) mg/ml in the treated group; this difference was not significant (p=0.64, Figure 3). In the placebo group there was no significant change in mean PC20 over 1 year (from 1.75 (0.32) mg/ml at the start of the study to 1.57 (0.28) mg/ml after 1 year (p=0.97)). Treatment induced changes in PC20 histamine were not significantly different between the two groups (p=0.77).

Quality of life

Overall quality of life scores were comparable at baseline in the placebo and in the treated group. The same was true for the subdomains. Clinically relevant improvements (difference >0.5)[18] were seen in breathing problems, physical problems related to chest problems, triggering/enhancing circumstances, and total score in both the treated and the placebo groups. Although the size of the improvements did not significantly differ between the two groups,

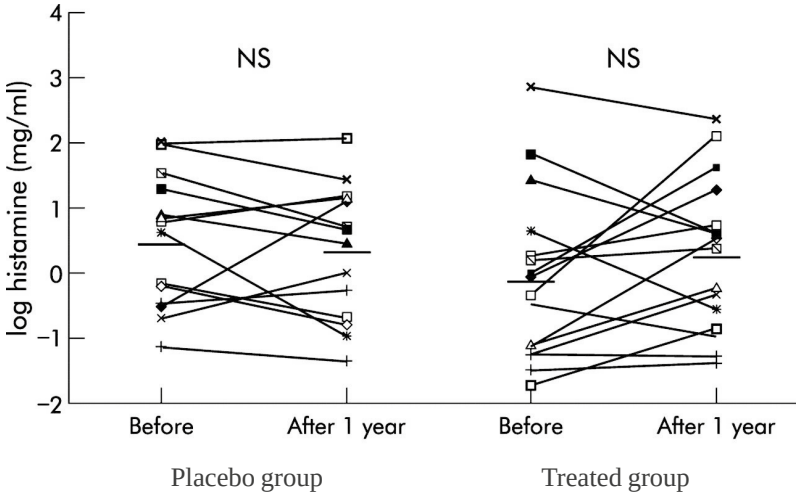

Figure 3 | Logarithmic PC20 histamine values before and after 1 year of intervention
(treated: – 0.11 v 0.28 mg/ml; placebo: 0.48 v 0.33 mg/ml). The geometric mean values of the groups are represented by horizontal lines.

Clinical parameters

Baseline values of asthma symptom scores showed no significant differences between the groups (Table 2). The median pulmonary symptom score did not change significantly over 1 year in either group. There was a significant decrease in the nasal symptom score in the treated group (p=0.04) but not in the placebo group; the difference between the two groups was not significant. Baseline PEF values (morning and evening) were comparable for both groups (Table 3). No significant changes in morning and evening PEF, peak flow variability, or the use of rescue medication occurred in either group following the 1 year intervention.

Table 2 | Symptom score before and after intervention (median values of 14 days of registration)

Placebo group			**Treated group**		
Patient	**Before**	**After**	**Patient**	**Before**	**After**
Pulmonary symptoms					
1	1.5	0.21	1	2.71	0.42
2	1.33	5.2	2	0.64	3
3	1.07	3.14	3	3.3	5.85
4	0.92	0	4	2.14	1.3
5	2.38	4.78	5	0.07	0
6	6.38	0.43	6	2	1.64
7	2	0.28	7	1.14	1.5

Placebo group			**Treated group**		
Patient	**Before**	**After**	**Patient**	**Before**	**After**
Pulmonary symptoms					
8	8.35	10.92	8	8.25	7.07
9	0.14	0.21	9	3.14	2.78
10	0.21	0.21	10	0.92	0.35
11	1.21	0.14	11	0	1.25
12	4.33	3.5	12	2.42	5.28
13	0.75	4.14	13	4	4.09
14	0	0	14	2.07	1.42
			15	0	0
			16	0	0
Median	1.27	0.36		2.04	1.46
Range	(00–8.35)	(00–10.92)		(00–8.25)	(00–7.07)
Nasal symptoms					
1	1.71	0.86	1	4.57	2.42
2	2.14	4	2	3.21	2.16
3	2.5	5.7	3	2.3	4.28
4	0	0	4	2.5	0.1
5	5	2.5	5	1.42	0.57
6	5.23	4.71	6	0.64	0.5
7	1	0	7	6.57	5.21
8	7.64	10.92	8	5	4.07
9	0.35	0.71	9	1.92	2
10	0.64	0.28	10	3.23	0.5
11	0.14	0	11	0	0
12	11.16	2	12	1.42	1
13	2.85	2.71	13	0.16	1
14	0	0	14	0.75	0.42
			15	0	0
			16	0	0
Median	1.93	1.43		1.67	0.79*
Range	(00–11.16)	(00–10.92)		(00–6.57)	(00–5.21)

*In the treated group significant difference after 1 year compared with before the intervention (p=0.04).

Table 3 | Peak flow values before and after intervention (median values of 14 days of registration)

Placebo group			Treated group		
Patient	**Before**	**After**	**Patient**	**Before**	**After**
Morning peak flow					
1	581	549	1	365	409
2	315	240	2	727	740
3	395	342	3	416	450
4	ND	ND	4	312	337
5	467	550	5	619	588
6	292	336	6	517	501
7	536	554	7	437	455
8	520	512	8	319	328
9	432	416	9	460	437
10	475	600	10	329	365
11	370	354	11	398	340
12	375	347	12	500	480
13	400	380	13	226	246
14	548	542	14	368	388
			15	476	446
			16	450	444
Median	432	416		426	440
Range	(292–581)	(240–600)		(226–727)	(246–740)
Evening peak flow					
1	563	553	1	396	406
2	288	236	2	683	748
3	434	343	3	516	470
4	ND	ND	4	346	390
5	509	565	5	634	601
6	289	326	6	502	506
7	534	592	7	444	456
8	529	516	8	380	374
9	431	406	9	399	411
10	625	700	10	370	386
11	351	362	11	400	351
12	375	346	12	497	484
13	380	400	13	225	247
14	556	552	14	362	360
			15	570	485
			16	449	440
Median	434	406		422	425
Range	(228–625)	(236–700)		(225–683)	(247–748)

No significant differences were seen between the groups.

Discussion

This study was performed to investigate the effect of anti-allergic mattress encasings in carpet free bedrooms on Der p 1 exposure in the bed and on clinical parameters in patients with moderate to severe asthma with allergy to house dust mite. We found a significant reduction in Der p 1 concentration in the dust collected from the mattresses in the actively treated group compared with the placebo group. PC20 histamine did not improve during the 1 year intervention period. Although a significant improvement in nasal symptoms and quality of life was observed only in the actively treated group, we found no significant difference between the placebo and actively treated groups in the change in pulmonary and nasal symptoms, quality of life, peak flow values, and use of rescue medication.

Earlier studies using several different types of mattress encasings have also shown a reduction in Der p 1 exposure on top of the mattress (Table 4) [8–10,19,20]. However, other studies did not show a reduction in Der p 1 concentrations and, remarkably, the carpets in the bedroom were not removed in these studies [21,22]. We excluded the problem of Der p 1 contamination from the floor13 by including only patients who had uncarpeted floors in their bedroom. This may have contributed to the fact that we could reach a significant reduction in the actively treated group even though we had higher baseline Der P 1 concentrations than other studies [22,23]. The reduction in allergen concentration was reached after 4 months and remained during the whole study period.

Although Der p 1 concentrations were significantly reduced in the actively treated group compared with the placebo group, we did not find a significant reduction in bronchial hyperresponsiveness. Other studies have also failed to demonstrate an improvement in bronchial hyperresponsiveness [10,11,22]. Two studies [22,23] did not find a substantial reduction in allergen concentrations in dust, which explains the lack of improvement in bronchial hyperresponsiveness. Frederick et al[10] stated that all patients were reasonably controlled on regular prophylactic treatment, so little or no change in clinical parameters could be expected. Even Cloosterman and coworkers[11] who tried to avoid this treatment effect by including only patients who either did not use inhaled steroids or were able to stop them, did not find a significant improvement in bronchial hyperresponsiveness nor in any of the clinical parameters used such as symptom score, PEF variability, and reversibility of FEV1.

How can we reconcile these observations? Patients participating in our study had severe hyperresponsiveness despite relatively high doses of inhaled corticosteroids of > 800 μg (for comparison, PC20 <4 mg/ml using the 30 minute method is comparable to 1 mg/ml in the 2

Table 4 | Overview of results and set up of controlled mattress cover studies

Study set up					Parameters						
Author	**No of patients**	**Age**	**Design**	**Duration (weeks)**	**Carpet**	**Acaricide**	**Der p 1**	**PC_{20} histamine**	**Symptoms**	**Peak flow**	**Medication**
Sarsfield[28]	14	Children	open c	52	–	–	+	ND	+	ND	ND
Murray[26]	20	Children	pl c	4	–	–	–	+	+	ND	ND
Walshaw[29]	50	Adults	pl c	52	+	–	+	+	+	ND	ND
Gillies[23]	24	Children	open c	12	+	–	–	–	–	ND	ND
Ehnert[8]	24	Children	open c	52	+	+	+	+	ND	ND	ND
Marks[22]	35	Adults	r c	26	+	+	–	–	–	–	ND
Weeks[20]	56	Children	r db pl	24	+	+	+	ND	ND	ND	ND
Carswell[19]	70	Children	r db pl	24	+	+	+	–	ND	–	ND
van der Heide[9]	59	Adults	open c	52	+	+	+	+	ND	ND	ND
Frederick[10]	31	Children	r sb pl	12	+	–	+	–	–	–	–
van der Heide[9]	45	Adults	open c	26	+	–	+	–	ND	ND	ND
Cloosterman[14]	29	Adults	r sb pl	6	+	+	ND	ND	+	–	ND
Sporik[21]	85	Children	open c	78	+	+	–	ND	ND	ND	ND
Cloosterman[11]	157	Adults	r db pl	20	+	+	+	–	–	–	ND

open c=open controlled; pl c=placebo controlled; r c=randomised controlled; r db pl=randomised double blind placebo controlled; r sb pl=randomized single blind placebo controlled; ND=not done; +=significant change; –=not significant change.

minute method). Thus, despite suppression of airway inflammation by use of inhaled steroids for years, severe hyperresponsiveness remained. Airway inflammation and bronchial hyperresponsiveness are induced by repeated inhalation of low doses of allergen [24]. However, a 1 year reduction in exposure to HDM might be too short in patients with a life time exposure before the intervention. One can hypothesise that the persistence of severe hyperresponsiveness is related to airway remodelling, the structural changes in bronchial architecture as a result of chronic airways inflammation [25]. No further improvement can therefore be expected with allergen reduction that most probably affects acute inflammation in this stage of already established disease.

Until now there have been no data available on the effect of allergen avoidance measures on quality of life. Clinically relevant improvements in quality of life were found in both groups. The instrument we used is a questionnaire specific for asthma and COPD. Our study focused on the allergic component of asthma which was represented by only three of the 55 items. This may partially explain the lack of difference between the two groups. Alternatively, allergen reduction may not affect quality of life, and the improvement in both the intervention and placebo groups may reflect the special attention received by the patient during the study period.

The important question in allergen avoidance studies is whether the avoidance technique used improves asthma control in sensitised patients [27]. Only a few double blind placebo controlled studies on allergen avoidance in relation to symptoms have been performed (Table 4). When reviewing these studies it is clear that improvement in symptoms occurred in four studies [14,26,28,29]. Two studied children [26,28], one studied patients with mild asthma, and one studied allergic patients who had not yet developed asthma (subclinical). Other studies [11,22], even in children [10,23], did not find a reduction in symptoms. PEF was recorded in seven studies; in two a significant increase in PEF occurred in patients with mild and preclinical asthma [14,29] while in five there was no significant increase in PEF [10,11,14,19,22]. Medication was recorded in one study without a positive result [10]. Taken together, the data suggest that the contribution of allergen avoidance measures is ineffective in patients with moderate to severe asthma. The severity of the clinical manifestation is influenced by more factors such as other allergens, viruses and air pollution, which are not influenced by the avoidance measures.

Surprisingly, there are no published reports of controlled trials of the effects of allergen avoidance on nasal symptoms. In our study rhinitis symptoms were scored in addition to asthma symptoms and we found a significant improvement in nasal symptoms in the treated group, although the difference between the two groups was not significant. The nose therefore seems to be more responsive to avoidance measures than the lower airways. A controlled trial of avoidance measures in patients with rhinitis using subjective and objective parameters might be of interest.

In conclusion, the use of anti-allergic mattress covers results in a reduction in Der p 1 concentrations in carpet-free bedrooms. In patients with moderate to severe asthma no change occurred in airways hyperresponsiveness and clinical parameters. This lack of effect may be due to the chronic stage of the asthma and/or limiting the avoidance measures to the bedroom. Future studies should explore whether night time and daytime avoidance measures in the early stages of the disease are more effective.

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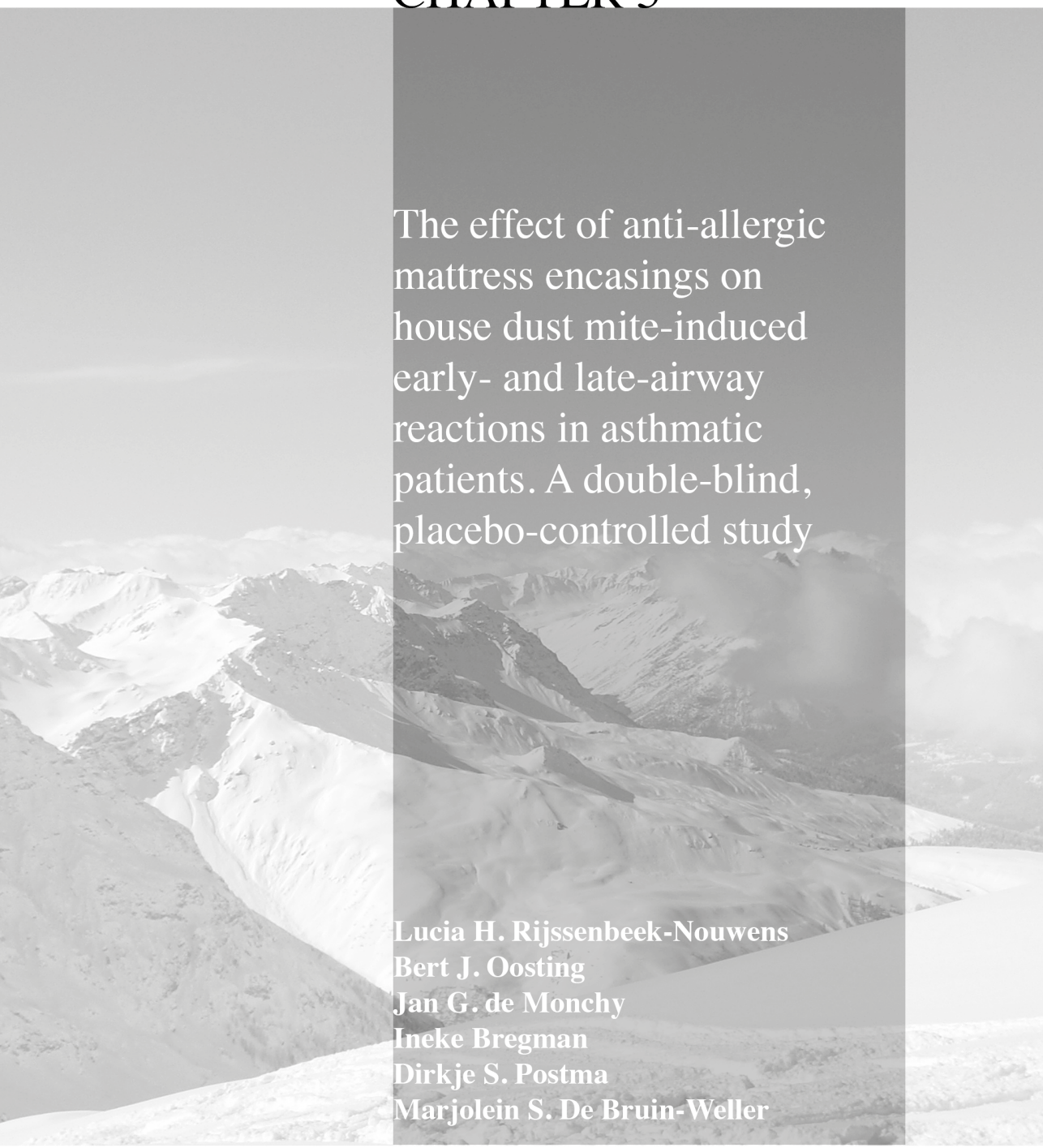
CHAPTER 5



The effect of anti-allergic mattress encasings on house dust mite-induced early- and late-airway reactions in asthmatic patients. A double-blind, placebo-controlled study

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Abstract

Background

Anti-allergic mattress encasing may provide clinical benefit in asthmatic patients. However, the effect of mattress encasings on allergen-specific parameters, such as bronchial reactions to house dust mite (HDM) challenge, is not clear.

Objective

To investigate the effect of anti-allergic mattress encasings on allergen sensitivity in patients with moderate to severe asthma.

Methods

Twenty-seven patients with asthma and HDM allergy were studied in a double blind, placebo controlled study. Concentrations of Dermatophagoides pteronyssinus (Der p 1) were measured in mattress dust before and after 1 year of treatment; bronchial histamine challenge, bronchial challenge with HDM and intradermal skin challenges with HDM were performed. The number of eosinophils in peripheral blood was assessed.

Results

In the active group, but not in the placebo group, there was a significant reduction in Der p 1 concentration in the dust collected from the mattresses after 1 year of treatment compared to before. There was a significant difference between the groups with respect to HDM-induced early-reaction (ER) in the airways and the number of blood eosinophils, which reflected an increase in ER and eosinophils in the placebo group without significant change in the active group. No significant improvement in PC20 histamine, late-reaction (LR) and skin tests was found in either groups.

Conclusion

Our data suggest that encasings protect against a further increase in allergen sensitivity in asthmatic patients, so their use should be recommended.

Introduction

Over the last decades, the prevalence and incidence of asthma have increased despite improved medical treatment. One of the contributing factors for this increase is thought to be exposure to allergens. House dust mite (HDM) has been proven to be one of the most important allergens. An association exists between the level of HDM exposure and the risk to develop asthma, i.e. the higher the exposure, the higher the risk [1-3]. Moreover, avoidance of HDM, as can be reached in the mountains or during hospitalization, can result in an improvement of asthma symptoms, peak flow values, non-specific hyper-responsiveness and the use of medication [4-6].

Allergen avoidance is the first step in the treatment of patients with allergic asthma. Several procedures have been developed to limit the exposure to HDM. Most procedures are expensive, require active participation of the patients and have not been extensively studied in double blind, placebo controlled studies. One such allergen avoidance measure is the application of encasings. Mattresses, pillows and bedding often contain large amounts of HDM, resulting in high exposure for several hours during the night. The use of specific anti-allergic mattress encasings can result in a strong reduction of Der p 1 levels on top of the mattress [7-9], with subsequent clinical improvement and a reduction in histamine-induced bronchial responsiveness in asthmatic patients [7,9]. These studies, however, have been generally performed in relatively mild asthmatics. In addition, there are no data on allergen-specific parameters, such as bronchial reactions to HDM challenge.

In the present study the effect of anti-allergic encasings was studied on bronchial response upon challenge with allergen as well as with histamine in patients with moderate to severe asthma in a double blind, placebo controlled design. In addition, other allergic parameters were studied, such as skin responsiveness to HDM, peripheral blood eosinophils and specific immunoglobulin (Ig)E to HDM.

Methods

Patients

Twenty-seven atopic, non-smoking patients with asthma and HDM allergy (10 females and 17 males, age 11–51 years) participated in the study. The clinical data are presented in Table 1. Although most patients had moderate to severe asthma, three patients in each group did not regularly use inhaled steroids. The patients were selected for increased bronchial responsiveness to histamine inhalation (PC20 < 4 mg/mL, 30 s inhalation of histamine phosphate solution), positive skin tests and/or elevated specific IgE to HDM allergen, early bronchial reaction to HDM inhalation and relevant HDM exposure on the mattress (> 1 μg Der p 1/g dust). All patients had FEV1 values >60% (predicted value). Pollen allergic patients were included and evaluated outside the pollen season. Patients did not have a history of respiratory tract infections in the previous six weeks or severe asthmatic attacks in the previous six months. Patients having a furred pet were only admitted when they had no pet allergy. None had received oral corticosteroids in the previous 6 months. All patients gave informed consent. The Medical Ethical Committee of Asthma Centre Heideheuvel, the Netherlands, approved the study.

Study design

The study was performed in a randomised placebo controlled, double blind, parallel group design, comparing the effect of allergen-impermeable encasings on the mattresses, pillows and comforters with matching placebo encasings during one year. At the start of the study a trained respiratory nurse visited the houses of the patients in order to establish allergen avoidance measures already present. All patients included in the study had bedroom floors without carpets. Patients were instructed to wash their sheets each week at 60°C. Apart from the mattress, pillow and comforter encasings no other allergen avoidance measures were taken. At the end of the study the nurse visited the houses again to verify that no other changes were made to the bedroom during the study. The patients were included continuously; the inclusion period lasted 2 years.

At the first visit patients underwent clinical evaluation. FEV1 and vital capacity (VC) values were measured, skin tests were performed and a PC20 histamine was assessed. Medication was withheld before the study period: inhaled steroids and sodium cromoglycate one week before the challenge, theophyllines, oral β2-adrenergic drugs, long-acting inhaled β2-adrenergic drugs and antihistamines 48 h before the tests and inhaled β2-adrenergic drugs 6 hours before the tests.

The patients continued their regular medication after the tests. The patients were told not

to change their medication during the intervention period and to record their medication use in an asthma diary.

Seventy-two hours after the bronchial histamine challenge the patients were admitted to the hospital for three consecutive days. On the first day, starting at 9.00 am, a challenge with a diluent control was performed. The second day, at 9.00 am, subjects underwent allergen challenge with HDM. Before the challenge blood sampling was performed for eosinophil counts. Spirometry was performed as on the first day. At the third day patients underwent a second histamine provocation.

Dust was collected from the mattresses of the patients for Der p1 measurement before installing the encasings. After 1 year the same test procedure was repeated and dust was collected on top of the mattress cover.

Collection and extraction of house dust

Collection of dust

Before, and at the end of the intervention, mattress dust was collected by a trained respiratory nurse using a vacuum cleaning apparatus (Philips type Vitall 377, 1300 watt, Eindhoven, the Netherlands). She vacuum cleaned the whole mattress during 2 min with a special filter device (Petersen-Bach A/S, Copenhagen, Denmark, mean pore size 5–6 μm, maximum pore size 10 μm). At the start of the study dust was collected directly from the mattress; at the end of the study dust was collected on top of the encasing, using always the same vacuum cleaner. The filters were stored in the freezer (−20°C) until analysis at the end of the study.

Der p 1 analysis

After sieving (0.35 mm), the amount of fine dust was weighed and a 10% (wt/vol) extraction in 0.01 mol/L NH4HCO3 buffer was performed by overnight rotation at 4°C. The samples were centrifuged and the supernatants were used for the measurement of Der p 1 concentration. Der p 1 antigen was measured using an enzyme-linked immunosorbent assay (ELISA). Monoclonal antibodies (ALK, Hørsholm, Denmark) against Der p 1 were immobilized on a 96-well plate. The incubation with the dust extracts was followed by a second incubation step with a polyclonal antibody (horseradish-peroxidase). After adding 1,2 phenyldiamine HCL as substrate the absorption at 490 nm was measured using an ELISA reader.

Histamine challenge

Histamine phosphate solutions (doubling concentrations from 0.25–32 mg/mL) were administered through a De Vilbiss 646 nebulizer with a gauged output of 0.13 mg/mL. The nebulizer was mounted to a valve box containing an aerosol filter. The nebulation time

was 30 s, during which the patient was instructed to breathe quietly. The test started with inhalation of a phosphate buffer aerosol. Prior to the inhalation three measurements of VC and FEV1 were performed (Jaeger Masterscreen; Breda, the Netherlands). FEV1 was measured after each doubling concentration. The PC20 histamine was derived by linear interpolation.

Bronchial allergen challenge

Allergen solutions were prepared from stock solutions of Dermatophagoides pteronyssinus in phosphate buffer solution (PBS) supplemented with 0.03% human serum albumin and 0.5% phenol (SQ 503, ALK Benelux, Houten, the Netherlands). Fivefold increasing concentrations of allergen solutions were prepared ranging from 80–10 000 BU/mL. The allergen solutions were administered through a De Vilbiss nebulizer mounted to a valve box containing an aerosol filter (output 0.13 mg/mL). The patients were instructed to breathe normally during 1 min for each dose. Increasing doses were given at 15-min intervals. The challenge procedure was terminated when the FEV1 value fell more than 15% below the baseline value. After the last inhalation FEV1 was recorded at 10-min intervals for the first hour, to determine the early asthmatic response and at 1-h intervals thereafter until 10 h after the last inhalation, to determine the late asthmatic response. FEV1 values were corrected for diurnal variation, determined during the previous day.

The cumulative provocation dose of allergen necessary to induce a fall in FEV1 value >20% from baseline (PD20 allergen) was calculated. This PD20 allergen is based on the observed maximal fall of FEV1 and the delivered dose of allergen, and characterizes the severity of the early and late asthmatic response [10,11].

Skin tests

Intradermal challenges (30 BU/mL, 0.03 mL) were performed on the back of the patients with a standardized HDM extract (ALK Benelux, SQ-503). The early response was scored as the weal diameter 15 min after challenge. Late responses were measured 6 h after challenge: indurations were determined according to a procedure suggested by Sokal [12]. The reactions on histamine and phosphate buffer diluent served as positive and negative controls.

Peripheral blood eosinophils

A blood sample was taken at 9.00 am at the start of the study and after 1 year. Blood eosinophils were counted using Bürker-Turk counting chamber (Landsmeer, the Netherlands).

Mattress encasings

In the active group, mattresses, pillows and bedding were encased using ACbTM Allergy Control covers supplied by Cara C'air (Velserbroek, the Netherlands). The same company made the matched placebo covers. The encasings were placed in position by a research nurse and left in situ for 1 year. The patients were advised to use their normal sheets on top of the mattress, pillow and comforter encasings and use no other additional bedding.

Data analysis

Statistical analyses were performed with SPSS 9.0 standard version. Comparisons within groups (before and after intervention) were made with the Wilcoxon signed rank test (WSR). Mann–Whitney U-test was used for between group comparisons. P-values <0.05 were considered significant. Data were log-transformed to obtain normal distribution, if necessary. The log-transformed data were analysed, using the sign test. These log-transformed values were expressed as mean value ± standard error of the mean (SEM).

Results

Demographic characteristics were similar between the two treatment groups (Table1). There were no significant differences between the two groups with regard to Der p 1 concentrations, PC20 histamine, PD20 allergen, skin tests, blood eosinophils, skin tests to HDM and medication use. Analyses of the diary cards at 0, 4, 8, 12 months showed that there was no change in medication during the study in both groups.

Table 1 | Clinical data of the patients

Patient	Age	Sex	FEV1 (% pred.)	PC20 hist. (mg/mL)	(Skin test *)	Rhinitis	Medication asthma	Medication rhinitis
Placebo								
1	21	M	97	1.76	2.1	–	B, SB	–
2	11	M	79	0.74	1.1	+	B, SB	–
3	19	F	111	1.00	1.4	+	SB	–
4	11	M	97	4.00	1.4	+	B, SB	–
5	29	M	81	0.33	1.2	–	F, SM	–
6	21	M	73	2.43	2.0	+	B, SB	B
7	27	F	70	0.90	1.2	+	B, SB	B
8	44	M	70	1.89	1.2	+	F, SM	F
9	17	F	138	1.78	1.9	+	–	B
10	40	M	64	1.13	1.6	+	B, SB	–
11	29	M	103	0.71	1.5	+	–	–
12	28	F	73	0.45	2.2	–	F, SB	–
13	12	M	106	4.00	1.6	+	B, SB	–
Mean	24		89	1.62	1.6			

Patient	Age	Sex	FEV1 (% pred.)	PC20 hist. (mg/mL)	(Skin test *)	Rhinitis	Medication asthma	Medication rhinitis
Active								
1	25	F	99	1.19	1.5	+	B, SB	–
2	29	M	99	0.95	1.6	–	B	–
3	41	M	67	3.79	2.2	+	B, SB	–
4	24	F	86	2.00	1.8	+	B, SB	–
5	31	M	81	1.22	1.5	–	–	–
6	24	M	80	0.55	1.1	+	B, SB	B
7	15	M	86	0.65	1.7	–	F	
8	22	F	104	2.67	1.4	+	B	–
9	51	F	70	0.45	1.2	+	B, SB	B
10	32	M	68	0.42	1.1	–	B, SM	–
11	36	F	103	0.35	1.8	+	SB	B
12	13	M	79	2.45	2.6	+	SB	–
13	42	M	75	0.42	1.2	–	B, SM	–
14	18	F	103	2.35	1.2	+	F, SM	F
Mean	29		86	1.39	1.6			

*, × times histamine reaction.

B, beclomethasone or budesonide; F, fluticasone; SB, salbutamol; SM, salmeterol; FO, formeterol

Der p 1 concentrations on mattresses

Figure 1 shows geometric mean Der p 1 concentrations on the mattresses before and 12 months after the start of the study in both groups. Der p 1 concentrations on the mattresses were significantly lower in the active group after 1 year (16.2 ± 6 and 2.2 ± 0.9 µg Der p1/g fine dust, respectively; p = 0.002). In the placebo group, there was no significant reduction in Der p 1 (26.4 ± 11.7 and 27.0 ± 12.8 µg Der p 1/g fine dust, respectively; p = 0.58). There was a significant difference in the treatment-induced change in Der p 1 concentration between the two groups (p = 0.04).

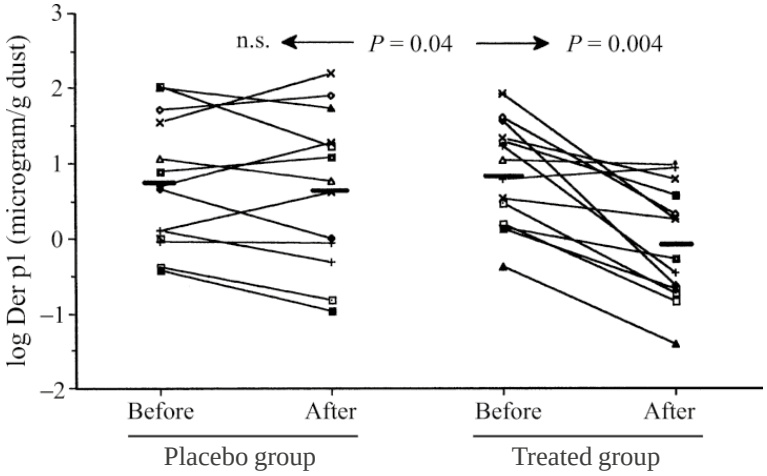

Figure 1 | Der p 1 concentrations on top of the mattress before and after 1 year of intervention: mean value (log data) of the groups is represented (Active: 0.85 and 0.06 µg Der p 1/g dust, respectively.
Placebo: 0.77 and 0.66 µg Der p 1/g dust, respectively). –= mean value, n.s. = not significant

Early and late asthmatic responses

In several patients the allergen concentration required to induce a fall in FEV1 of at least 20% differed during the study. Therefore, the early and late responses on HDM challenge were expressed as PD20 allergen.

PD20 early response

Figure 2(a) shows the PD20 allergen of the early response before and 1 year after the intervention. All patients showed early response before treatment. In the active group, there was no significant change in PD20 allergen before and after 1 year (750 ± 175 BU/mL and 611 ± 157 BU/mL, respectively: p = 0.79) In the placebo group, the PD20 allergen after 1 year was significantly lower compared to before (PD20 1580 ± 646 BU/mL and 473 + 161 BU/mL, respectively; p = 0.003), indicating a more sensitive response after 1 year. There was a significant difference in the treatment-induced change in PD20 allergen between the two groups (p = 0.04).

PD20 late response

Figure 2(b) shows the PD20 allergen of the late response before and 1 year after the intervention. Late-phase reactions could be demonstrated in ten patients in the placebo group and in nine patients in the active group.

There was no significant change in PD20 allergen during the year in the active group (PD20 498 ± 111 BU/mL and 360 ± 84 BU/mL, respectively; p = 0.51). In the placebo group there was a significant decrease in PD20 allergen after 1 year compared to before (PD20 1103 ± 385 BU/mL and 394 ± 144 BU/mL, respectively; p = 0.002). The treatment-induced change in PD20 allergen between the two groups was not significant (p = 0.11).

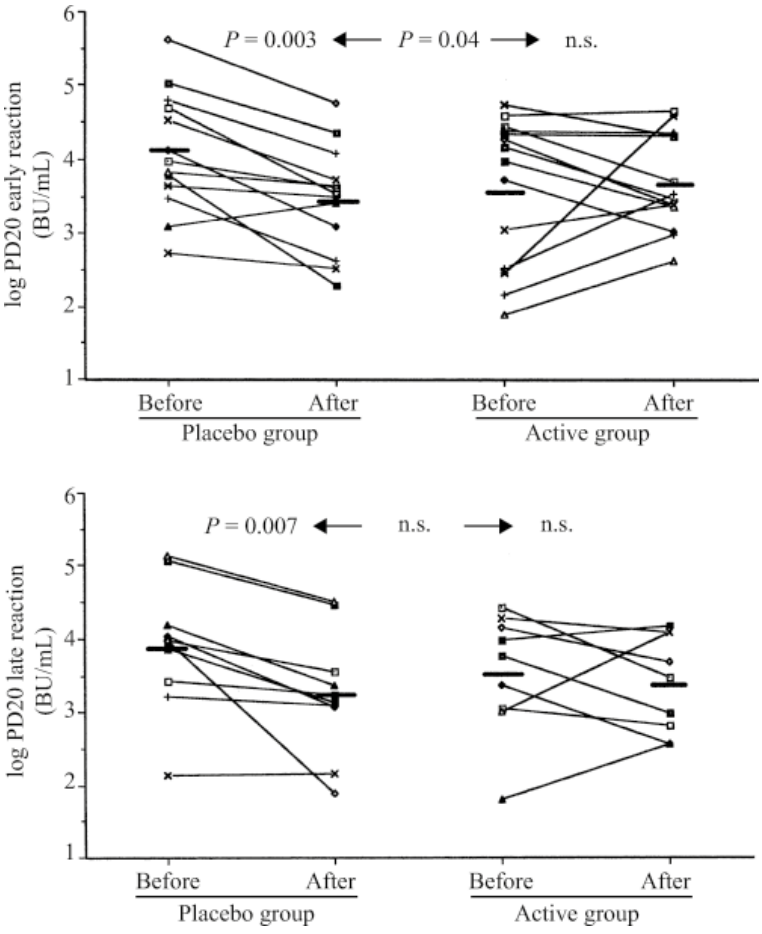

Figure 2a | The effect of mattress encasings on PD20 of early asthmatic response; mean value (log data) of the groups is represented (active: 3.62 and 3.69 µg BU/mL, respectively.

Placebo: 4.10 and 3.47 BU/mL, respectively).

Figure 2b | The effect of mattress encasings on PD20 of late asthmatic response; mean value (log data) of the groups is represented (active: 3.53 and 3.38 BU/mL, respectively.

Placebo: 3.90 and 3.25 BU/mL, respectively). Only the results of patients who showed a late-phase response are represented. –= mean value, n.s = not significant

PC20 histamine

Mean log PC20 histamine in the active group was 0.24 ± 0.31 mg/mL at the start of the study and 0.32 mg/mL ± 0.29 after 1 years, the difference being not significant (p = 0.18) (Fig. 3). In the placebo group, there was no significant change in PC20 histamine during one year (mean log PC20 histamine before 0.36 mg/mL ± 0.28; after 1 year 0.39 mg/mL ± 0.28: p = 1.0). The treatment-induced change in PC20 histamine between the two groups was not significant (p = 0.77).

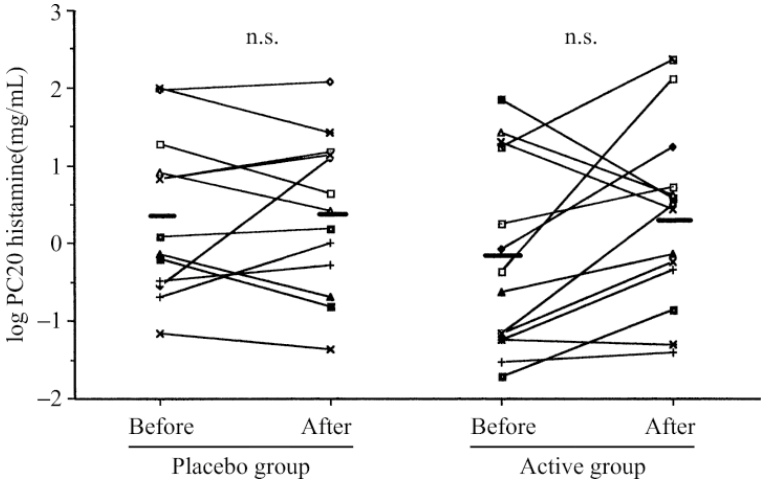

Figure 3 | PC20 histamine before and after 1 year of intervention; mean value (log data) of the groups is represented (active: -0.36; 0.44 mg/mL, respectively.
Placebo: 0.36; 0.39 mg/mL, respectively). –= mean value, n.s. = not significant.

Skin reactions

Early reactions

Figure 4(a) shows the results of the early skin reactions after intradermal allergen challenge before and after 1 year in both groups. There was no significant change in skin reaction during 1 year in the active group (18.5 ± 1.3 mm and 16.1 ± 0.9 mm, respectively; p = 0.12). This was also the case in the placebo group (18.7 ± 1.8 mm and 17.2 ± 1.8 mm, respectively; p = 0.58). The treatment-induced change in early skin reaction was not significantly different between the two groups (p = 0.66).

Late reactions

There was no significant change in skin reaction over 1 year follow-up both in the active group (18.0 ± 2.4 mm and 13.5 ± 2.2 mm, respectively; p = 0.20) and in the placebo group (12.9 ± 1.9 mm and 13.6 ± 1.2 mm, respectively; p = 0.58) (Figure 4b). The treatment-induced change in early skin reaction was not significantly different (p = 0.57) between the two groups.

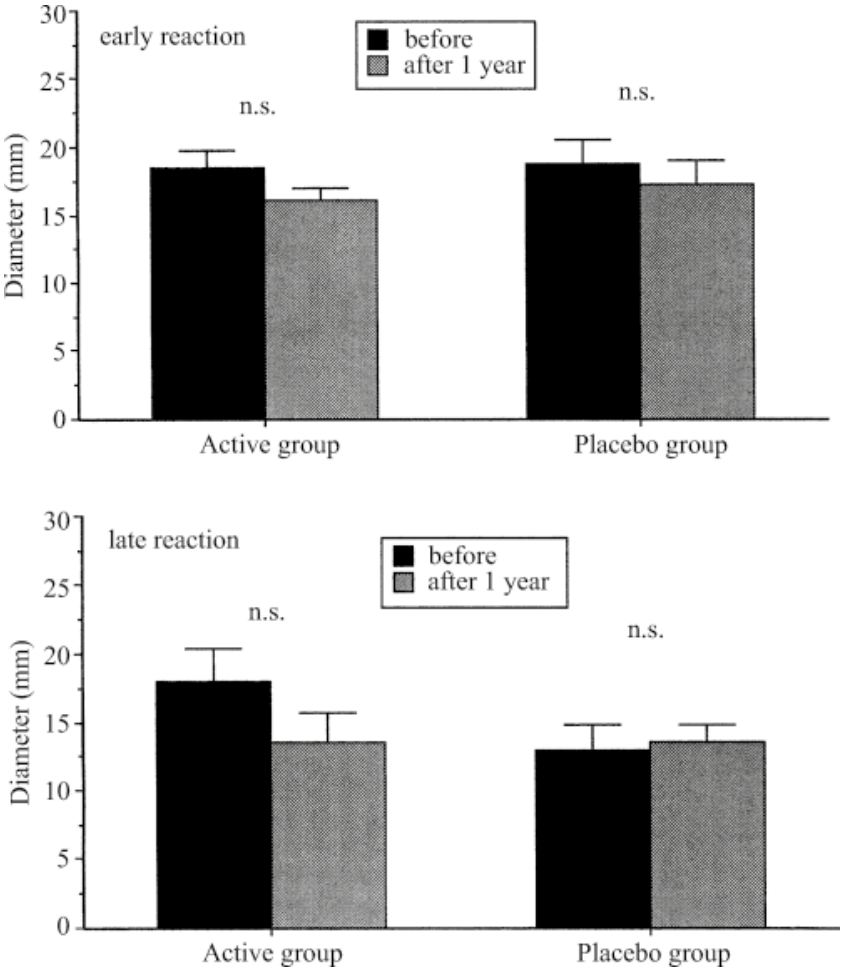

Figure 4 | Early (a) and late (b) skin reaction before and after 1 year of intervention (mm)

Specific IgE

There was no significant change in the level of specific IgE after 1 year compared to before in the active group (54.1 ± 10.1 PRU/mL and 44.3 ± 10.4 PRU/mL, respectively; p = 0.13), neither in the placebo group (59.2 ± 112.6 PRU/mL and 53.3 ± 10.0 PRU/mL, respectively; p = 0.20).

The treatment-induced change in specific IgE was not significantly different (p = 0.93) between the two groups.

Peripheral blood eosinophils

Total blood eosinophil counts did not significantly change after 1 year in the active group (382 ± 47 × 106 L and 366 ± 50 × 106 L, respectively; p = 0.66). In the placebo group total blood eosinophil counts were significantly higher after 1 year compared to before (273 ± 37 × 106 L and 436 ± 69 × 106 L, respectively; p = 0.03). There was a significant difference in the treatment-induced change in number of blood eosinophils (p < 0.05)(Figure 5).

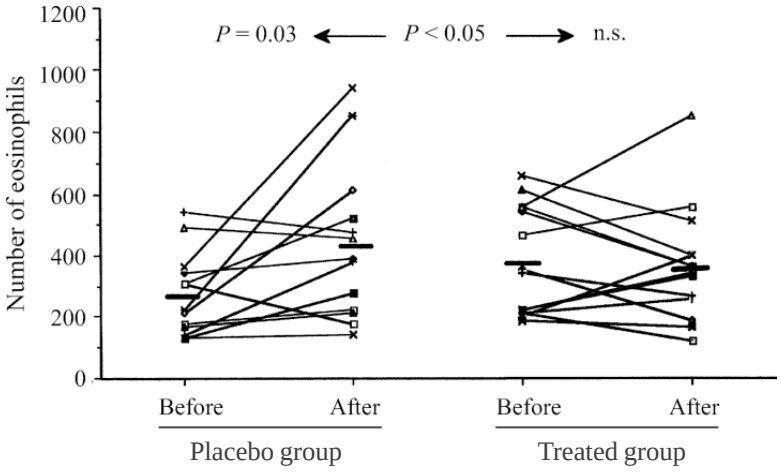

Figure 5 | The effect of mattress encasings on the number of peripheral blood eosinophils (106 L). –= mean value, n.s = not significant

Discussion

The present study was performed in order to investigate the effect of anti-allergic mattress encasings on allergen sensitivity in patients with moderate to severe asthma and HDM allergy. We found a significant reduction in Der p 1 concentrations in the dust collected from the mattresses in the active group, which was also significantly different from the placebo group. There was a significant difference in ER to allergen and number of peripheral blood eosinophils between the active and the placebo group. This difference reflected increases in ER and the number of eosinophils in the placebo group, whereas no change occurred in the treatment group. No significant differences between the groups occurred with respect to PC20 histamine, late bronchial reaction, skin test responsiveness and specific IgE.

It has been demonstrated that higher exposure to HDM is associated with more severe asthma [13-16]. In an attempt to maximally reduce the HDM exposure at home, several combinations of avoidance measures have been studied [6,17,18]. These studies are difficult to compare, because of the large differences in applied avoidance measures (often combination of chemical and physical methods), outcome parameters, study population and design.

In the Netherlands, mattresses and bedding are a major source of HDM and the use of anti-allergic encasings has become a standard procedure in the treatment of HDM-allergic asthmatic patients. Therefore, we have chosen to focus solely on the additional effect of mattress, pillow and bedding encasings, leaving other allergen avoidance measures unchanged. In addition we have chosen to investigate a population of patients with severe bronchial hyper-responsiveness despite the use of inhaled bronchial corticosteroids.

In our study we found a significant reduction in Der p 1 concentrations on the mattresses in the active group after 1 year of intervention. The placebo encasings used in the study had a similar appearance as the active encasings, but did not protect against allergen exposure, as Der p 1 concentrations remained the same after 1 year. We have chosen 1 year of intervention to exclude seasonal variations in Der p 1 exposure, because seasonal variation in mite levels may easily exceed a factor of two or three when winters are relatively cold [15,19].

Some earlier studies using several different types of mattress encasings have also shown a reduction of Der p 1 exposure on top of the mattress [7-9, 20,21]. Van der Heide et al. [9] showed the decrease in Der p 1 on the mattresses to be greater with mattress encasing than with acaricide treatment. In contrast, when combining impermeable covers over mattress, pillows and duvet with tannic acid/acaricidal spray on the carpets and furniture, Marks et al. found a 29% reduction in HDM allergen levels on the beds after two weeks but after 3 and 6 months the reduction in Der p 1 concentrations was not significant anymore [22].

The authors suggested that in a high HDM environment simple chemical treatment and encasement of bedding is not sufficient to cause a sustained beneficial reduction in allergen levels. Our study was performed in a high HDM environment as measured by Der p 1 concentrations on the mattress and showed a significant reduction in HDM. The difference between the studies is the presence of carpets on the floors in the study by Marks and the absence of carpets in our study. The above data combined suggest that encasings are effective in HDM reduction, provided that carpeting is avoided.

In the present study the significant reduction in Der p 1 exposure in the active group was not associated with significant effects on histamine-induced hyper-responsiveness. Other studies showed variable results with respect to effects on hyper-responsiveness [8,9,21-24]. This may be due to the duration of use and the effect of encasings; the study duration seems not essential since both short-term (12 weeks−6 months) and long-term studies [9, 25] have shown beneficial effects [9,25]. The severity of asthma may have affected the outcome of the studies. Studies with a positive effect concerned patients with mild to moderate asthma [7]. For instance van der Heide et al. [9] included patients with a PC20 <32 mg/mL (mean value 3.82 mg/mL), we included patients with severe hyper-responsiveness (PC20 <4 mg/mL, mean value 1.39 mg/mL). Finally, mattress encasings reduce HDM exposure during the night, yet patients may still be exposed to relatively large amounts of HDM from other sources during the day. All studies so far have not measured these confounding factors. In addition, the severity of hyper-responsiveness is also determined by other factors such as other allergens [26-30], viruses and air pollution, which are not influenced by the avoidance measures. Especially in patients with more severe asthma the relative contribution of the night-time HDM exposure on the level of hyper-responsiveness may be limited.

We evaluated the effects of allergen avoidance on allergen-specific parameters in the airways, skin and peripheral blood. We did not find effects on early and late skin reaction to HDM nor on HDM-specific IgE in peripheral blood after 1 year of intervention. This is compatible with the data of Wickman et al. who also found no change in the degree of allergen sensitization assessed by skin prick tests or specific IgE antibodies against Der p 1 of Der f 1 after 18 months of HDM avoidance measures including mattress encasings [31]. Other studies also showed that the use of mattress encasings did not reduce total IgE, allergen-specific IgE or skin test sensitivity to HDM, despite the reduced HDM exposure [9,32].

Our study is, to our knowledge, the first to evaluate the effects of mattress encasings on allergen sensitivity in the airways. We could not demonstrate an increase in PD20 allergen, both in the early- and late-response after bronchial challenge with HDM, in the active

group. In the placebo group, however, both ER and LR PD20 allergen, significantly decreased after 1 year compared to before, indicating an increase in allergen sensitivity. The difference between the groups was significant for the ER. This finding is difficult to explain. The increased allergen sensitivity cannot be explained by an increase in allergen exposure or an increase in hyper-responsiveness, because these parameters did not change in the placebo group. Changes in PD20 cannot be explained by changes in PC20 histamine alone [33]. Furthermore, the use of medication was unchanged in both study groups. The only parameter that changed during the study was Der p 1 exposure, which was significantly reduced on the beds of the patients in the active group. This might suggest that a reduction in Der p 1 exposure after the use of the anti-allergic mattress encasings may prevent a further deterioration in lower airway allergen sensitivity, as seen in the placebo group.

Another surprising finding was the significant increase in the number of peripheral blood eosinophils in the placebo group after 1 year which was not seen in the active group. Also this difference between the groups can only be explained by differences in allergen exposure. The significant increase in blood eosinophilia in the placebo group was associated with an increase in airway allergen sensitivity, but not with an increase in hyper-responsiveness. This latter finding is in contrast with other studies showing a positive correlation between blood eosinophilia and hyper-responsiveness [34], though in a cross-sectional way.

The present study showed that the use of anti-allergic mattress encasings in patients with moderate to severe asthma did not result in a reduction in hyper-responsiveness or airway allergen sensitivity, despite a significant reduction in Der p 1 exposure. It is possible that the limited efficacy is due to the severity of asthma in our study population. Since our data suggest that there is some protective effect against further increase in airway allergen sensitivity, the use of anti-allergic mattress encasings in this population should still be recommended.

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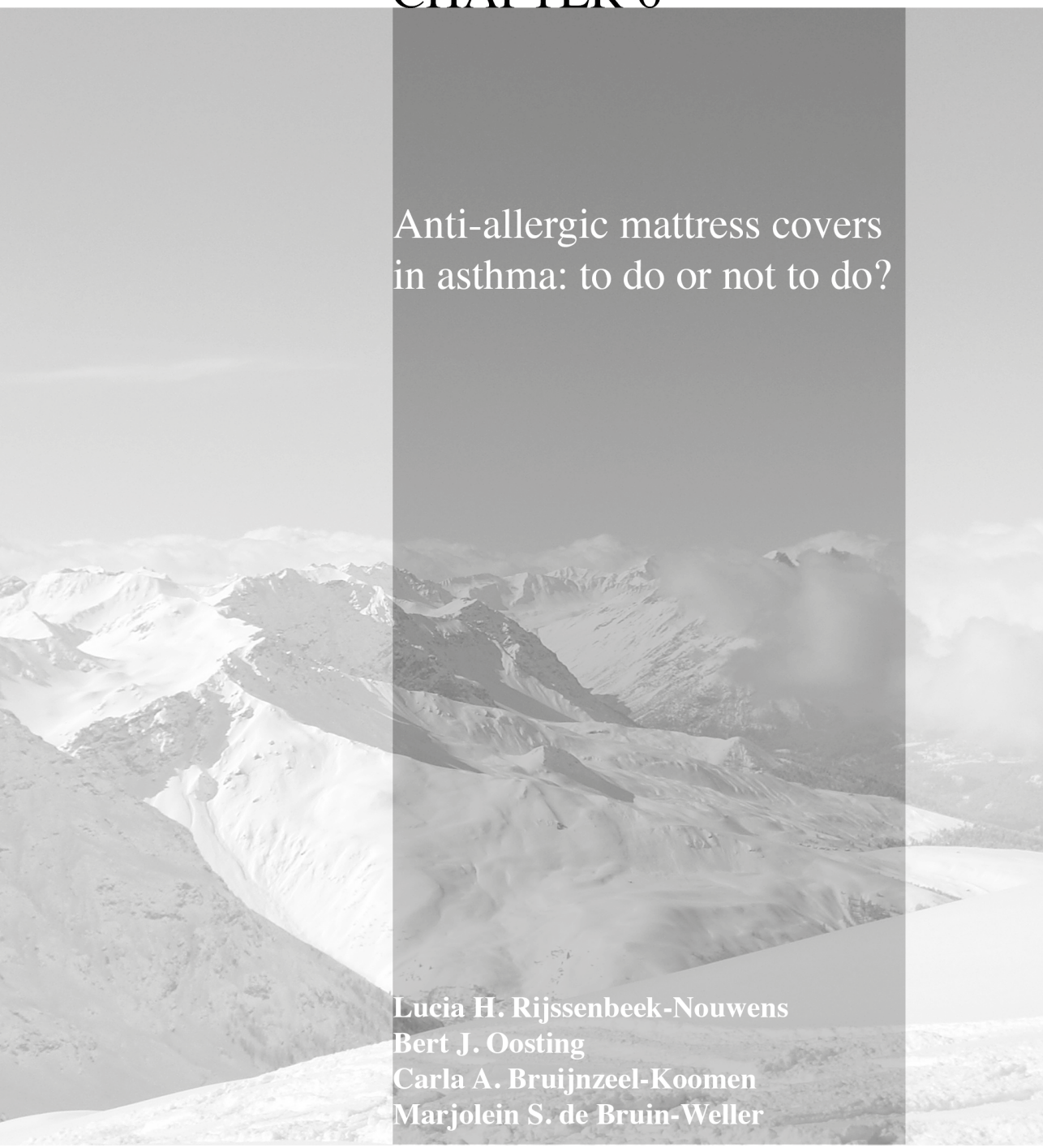
CHAPTER 6



Anti-allergic mattress covers in asthma: to do or not to do?

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Introduction

Although early studies on mite-impermeable mattress covers suggested clinical benefit in asthma[1,2], other double blind placebo controlled studies show less favourable results [3,4]. The results of the study by Luczynska et al.[5] published in this issue of the journal lack evidence of clinical benefit in mild-to-moderate asthmatic patients, despite a decrease in allergen load. These findings seem to be in contrast to the fact that house dust mite (HDM) allergen has proved to be an important trigger in allergic asthma.

From a number of cross-sectional and longitudinal studies, it can be concluded that there is a very close association between HDM exposure and HDM sensitization[6]. In addition, HDM exposure in already sensitized individuals can trigger an exacerbation of asthma, and prolonged exposure can lead to the persistence of symptoms[7]. Asthma is usually more severe in sensitized patients who are exposed to higher allergen levels[8].

There is clear biological plausibility for the role of HDM allergens, in that the proteolytic activity of their enzymes can actively damage the airway epithelium. In effectively mite allergen-free environments, as in hospitals[9] or in high-altitude Alpine clinics[10], the condition of asthmatic patients improves both symptomatically and in terms of non-specific bronchial responsiveness. Even 1 month at high altitude can result in a reduction in airways inflammation, measured as adenosine 5′-monophosphate (AMP), bronchial hyper-responsiveness (BH), blood eosinophils and eosinophilic cationic protein (ECP)[11]. Ten weeks of high-altitude allergen avoidance in adolescent patients with persistent asthma, despite treatment with high-dose inhaled corticosteroids, resulted in improvement of asthma, assessed by clinical and inflammatory markers of disease severity. These findings indicate that short-term rigorous allergen avoidance can improve the control of severe asthma over and above what can be achieved by high doses of inhaled steroids[12].

Although it is impossible to achieve such low levels of HDM exposition at sea level as at high altitude, in the past much effort has been put in attempts to reduce HDM exposition in the home environment. Methods such as extensively vacuum cleaning, use of acaricides, air filters, ventilation, smooth floors, removing carpets and curtains, etc. have been used in order to reduce HDM exposition.

Reduction of allergen exposure in the bedroom and the bed is considered to be the primary target of avoidance measures, since the bed is the most important habitat and source of mite allergens to which we are exposed for many hours during sleep.

The most effective avoidance measure is to cover the mattress, pillows and duvets with mite allergen-impermeable covers[1–3] and washing all bedding in hot temperature[13]. Covering the mattresses, pillows and duvets is a relatively simple method that can substantially reduce night-time HDM exposure. Its efficacy can be studied in a placebo-controlled manner. Therefore, over the past few years many studies have focused on this subject.

Anti-allergic mattress coverings: secondary prevention

In some studies, anti-allergic covers are combined with the use of acaricides. Overall, it is difficult to compare the results of the different studies because of large differences in study design, study population (children vs. adults, differences in disease severity) and outcome measures.

Part of the confusion is resolved by distinguishing clearly between two measures of effectiveness: reduction in allergen exposure (efficacy) and impact on symptomatic illness (clinical effectiveness)[14]. It is not surprising that interventions that lack efficacy are clinically ineffective. In a narrative review, Custovic et al.[15] examined 31 studies in which mattress covers, in some cases combined with acaricides, were used. However, only nine of these reported a significant reduction in mite counts and/or mite allergen level. In three of these nine studies, the period of treatment was too short (8–12 weeks). In the remaining six studies, which were controlled studies (6–12 months), a significant reduction in allergen load was accompanied by clinical improvement such as a significant improvement in lung function, symptoms, medication use and/or BH. In a quantitative meta-analysis, Gotzsche et al.[16] included 23 studies of chemical and physical methods aimed at reducing HDM exposure among asthmatic patients who were sensitive to mites. This meta-analysis focused on asthma symptoms and peak flow, and was unable to show an overall significant improvement in these clinical outcome measures. Only six of the 23 methods studied adequately reduced levels of mite allergen: these methods concerned physical (encasings) or combined physical and chemical (acaricides). In the subgroup of trials that reported a successful reduction in the population of mites, the results were similar to the overall results. This meta-analysis only looked at the asthma symptom scores and peak flow rates, although these were not the primary outcomes of the successful studies.

In 2001, the Cochrane Review on HDM control measures for asthma was published[17]. The objective of this review was to assess the effects of reducing exposure to HDM antigens in the homes of mite-sensitive asthmatics, assessing chemical and physical methods separately and together. Randomized trials of mite-control measures vs. placebo or no treat-

ment in asthmatic patients sensitized to HDM in the period 1973–1999 were searched.

Twenty-nine trials (939 patients in the analyses) were included. Nine trials assessed chemical methods alone, 15 physical methods alone and five a combination of chemical and physical methods.

Overall, there was no statistically significant difference in improvement of asthma, asthma symptom scores, medication usage or peak flow in the morning between the intervention and control group. For chemical methods used alone, there was a statistically significant adverse effect on symptoms ($p=0.03$) compared with placebo, whereas for physical methods used alone, as evaluated in parallel group trials, there was a statistically significant beneficial effect ($p=0.02$).

Looking at the 20 trials using physical methods (with or without chemical methods), only seven trials showed a significant reduction in HDM exposition.

The authors conclude that overall, the trials of current chemical and physical methods aimed at reducing exposure to HDM allergens failed to show an effect on clinical outcome measures. The explanation that they find most plausible is that the methods reviewed did not adequately reduce mite antigen levels, i.e. had no efficacy. They pose that currently available evidence does not provide a secure basis for advice and policy concerning prescription of encasings.

Table 1 summarizes more recent double blind, placebo controlled studies in atopic patients performed after 1998. Three studies have focused on atopic dermatitis patients[18–20] showing conflicting results. In allergic rhinitis patients, Terreehorst et al.[21] could not demonstrate significant clinical improvement, despite a significant reduction in Der p 1 and Der f 1 allergens. Clinical effectiveness in asthmatic patients could not be demonstrated in most studies[22–24]; only one study reported a significant decrease in the dose of inhaled steroids in children[25].

In a recent large multi-centre study in 1122 adult asthmatic patients, allergen-impermeable bed covers as a single intervention method did not result in clinical improvement in adult patients with asthma[26]. Surprisingly, the peak expiratory flow rate significantly improved in both groups, suggesting a large placebo effect. The prevalence of HDM sensitivity in this study was only 65% in both groups; there was no difference in the pattern of improvement between the mite-sensitive patients and those who were not sensitized to mites.

Another surprising finding was that the concentration of Der p 1 in the mattress dust showed no significant difference between the active and placebo groups at 12 months. The authors suggest that the total amount of allergen recovered would more adequately

reflect the effect of the intervention than the allergen concentration.

Subsample analysis was performed in two patient groups who were expected to benefit most from HDM avoidance methods: patients with high sensitivity to mite allergen and patients with a high baseline level of mite allergen in their mattress. Also, in these subgroups no significant clinical improvement could be demonstrated. The authors concluded that dust-mite allergen-impermeable covers are clinically ineffective for routine management of adult asthma in the absence of other mite-control measures.

Primary prevention

In Berlin, a cohort of 1314 new born babies was followed for 3 years. Children who were sensitized in the first 3 years of life were exposed to significantly higher HDM concentrations. From this study, it was concluded that avoidance measures in the domestic environment aimed at the primary prevention of allergen-driven sensitization should be introduced at the earliest possible stage, if possible during infancy[27].

The Manchester Asthma and Allergy study showed in a prospective, prenatally randomized way that it is possible to achieve and maintain a low mite allergen environment during pregnancy and the first year of life in homes of infants at risk of atopy[28].

However, evidence for indoor allergen exposure being a primary cause in the development of asthma is not so clear. Data from Germany[29] do not support the hypothesis that exposure to environmental allergens directly causes asthma in childhood, but that induction of specific IgE responses and the development of childhood asthma are determined by independent factors. Since allergic asthma seems to be a Th2 disease, immunomodulating factors such as early childhood infections, lipopolysaccharide exposure or other factors influencing gene–environment interaction and individual susceptibility seem to be relevant for the development of childhood asthma.

Apart from allergen sensitization and exposure, a number of factors are associated with increased incidence of asthma: reduced exposure to infection and to farm animals in early childhood and maternal smoking[30].

The first results of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA birth cohort study) study showed that the use of HDM-impermeable mattress covers on the child's and parents' beds reduced night cough, but not other respiratory symptoms, atopic dermatitis and atopic sensitization in the first 2 years of life [31].

Tertiary prevention

Is it possible that HDM avoidance measures, such as anti-allergic mattress coverings, prevent further deterioration of already established disease in HDM-sensitized patients?

In patients with moderate-to-severe asthma (severe hyper-responsiveness despite relatively high doses of inhaled corticosteroids), the effect of mattress encasings on allergen sensitivity in the airways was studied in the Netherlands[32]. Bronchial challenges with HDM were performed before and after 1 year of intervention. During the study period, the dose of inhaled steroid remained unchanged. In the placebo group, bronchial allergen challenge after 1 year resulted in a significant decrease in PD20 allergen, indicating a significant increase in allergen sensitivity. No significant change in Der p 1 concentration in the dust collected from the mattresses was found after 1 year compared with before. In the actively treated group, the PD20 allergen remained unchanged, while there was a significant decrease in Der p 1 concentration in the dust collected from the mattresses. In addition, the significant increase in blood eosinophils seen in the placebo group after 1 year compared with before was not seen in the actively treated group. The only parameter that changed during the study was Der p 1 exposition.

These data suggest that anti-allergic mattress coverings may have some protective effect against further increase in airway allergen sensitivity.

Summarizing the large amount of data from the literature, it seems that the use of anti-allergic mattress covers as a solo intervention in allergic asthma does not result in clinical benefit. On the other hand, the relationship between HDM exposure and asthma severity has often been established.

How can we reconcile these observations?

Although in most studies the night-time exposure to HDM was significantly reduced, patients can still be exposed to large amounts of HDM during daytime, in other parts of the house, at work, during social events, etc. As was stated earlier, the extremely low levels of HDM exposure, as at high altitude cannot be reached at sea level.

More rigorous allergen avoidance methods focused on both the home and working environments may have some clinical benefit; however, double-blind placebo-controlled studies are not possible.

In addition, in allergic asthma severity is influenced by factors other than HDM exposure, including other allergens, viruses and air pollution, which are not influenced by the avoidance measures. Furthermore, in more advanced stages of allergic asthma chronic inflammation results in structural changes in bronchial architecture [33], processes that cannot be reversed by allergen avoidance.

The question remains: anti-allergic mattress coverings: to do or not to do? What should we advise the 'workers in the field'?

First it is important that the patients receive optimal treatment for their disease, including medication, education in asthma management and instruction in how to avoid risk factors, such as smoking, emotional stress, etc [34]. When patients do not receive optimal treatment, allergen avoidance measures are useless!

Second, in HDM-allergic patients who receive optimal treatment, allergen avoidance measures should not be limited to the sleeping room alone, but should include patients' home and working environments.

Anti-allergic mattress covers may then have an additional effect on the patient's well being, and perhaps may in part prevent further deterioration of the disease.

Table 1 | Published randomized controlled trials from 1998 to 2003 looking at the effect of avoidance measure on clinical outcome variables of the atopic syndrome

Author	Study design and duration	Avoidance measures	Effect on mite/allergen	Clinical outcome
Friedman and Tan [18]	RDBP; 6 months; *n*=48, adults, AD	Encasing, vacuum cleaning, acaricide spray	Significant reduction in dust weight	Improvement of eczema scores ($P<0.0006$)
Gutgesell et al. [19]	RCT; 12 months; *n*=12, adults, AD	Encasing, acaricide spray	Significant reduction in Der p 1	No effect on SCORAD (AD score) and ECP levels
Rijssenbeek-Nouwens et al. [31]	RDBP; 12 months; *n*=27, adults, AA	Encasing	Significant reduction in Der p 1	Significant increase in HDM-induced early reaction during bronchial challenge in placebo group combined with a significant increase in number of blood eosinophils, no effect in active treatment group.
Sheikh et al. [22]	RDBP; 6 months; *n*=47, children (5–14 years), AA	Encasing	Not measured	No effect on peak expiratory flow, asthma symptom scores, medication usage and asthma consultations
Koopman et al. [23]	RDBP; 24 months; *n*=1282 allergic pregnant women, effect on their children (0–2 years) was measured, AA, AD	Encasing	Reduced HDM levels	No effect on respiratory symptoms, atopic dermatitis and atopic sensitization
Rijssenbeek-Nouwens et al. [24]	RDBP; 12 months; *n*=30, adults, AA, AR	Encasing	Significant reduction in Der p 1	No effect on PC_{20} histamine, QoL, asthma and nasal symptom scores between the groups Improvement of nasal symptom scores in active treatment group compare with before treatment

Author	Study design and duration	Avoidance measures	Effect on mite/allergen	Clinical outcome
Oosting et al. [20]	RDBP; 12 months; *n*=86, adults and children (8–50 years), AD	Encasing	Significant reduction in Der p 1+Der f 1	No effect on LSS (AD score)
Halken et al. [25]	RDBP; 12 months; *n*=60, children (6–15 years), AA	Encasing	Significant reduction in HDM allergens	Significant decrease in the dose of inhaled steroids
Brunekreef et al. [34]	RDBP; 3 years; *n*=855, pregnant women and their children (3 years)	Encasing	Significant reduction in HDM allergens	No clinical improvement
Woodcock et al. [26]	RDBP; 12 months; *n*=1122, adults, AA	Encasing	No significant reduction in HDM allergens	No clinical improvement (mean morning expiratory flow rates) between the groups
Terreehorst et al. [21]	RDBP; 12 months; *n*=279, adults and children (8–50 year), AR	Encasing	Significant reduction in Der p 1+Der f 1	No clinical improvement (nasal allergen provocation testing and rhinitis-specific visual-analogue scale, daily symptom scores)

RDBP, randomized double-blinded placebo-controlled trial; RCT, randomized controlled trial; ECP, eosinophilic cationic protein; LSS, least significant score; AA, allergic asthma; AD, atopic dermatitis; AR, allergic rhinitis; HDM, house dust mite; Der p 1, major allergen of the Dermatophagoides pteronyssinus; Der f 1, major allergen of the Dermatophagoides farinae; QoL, quality of life.

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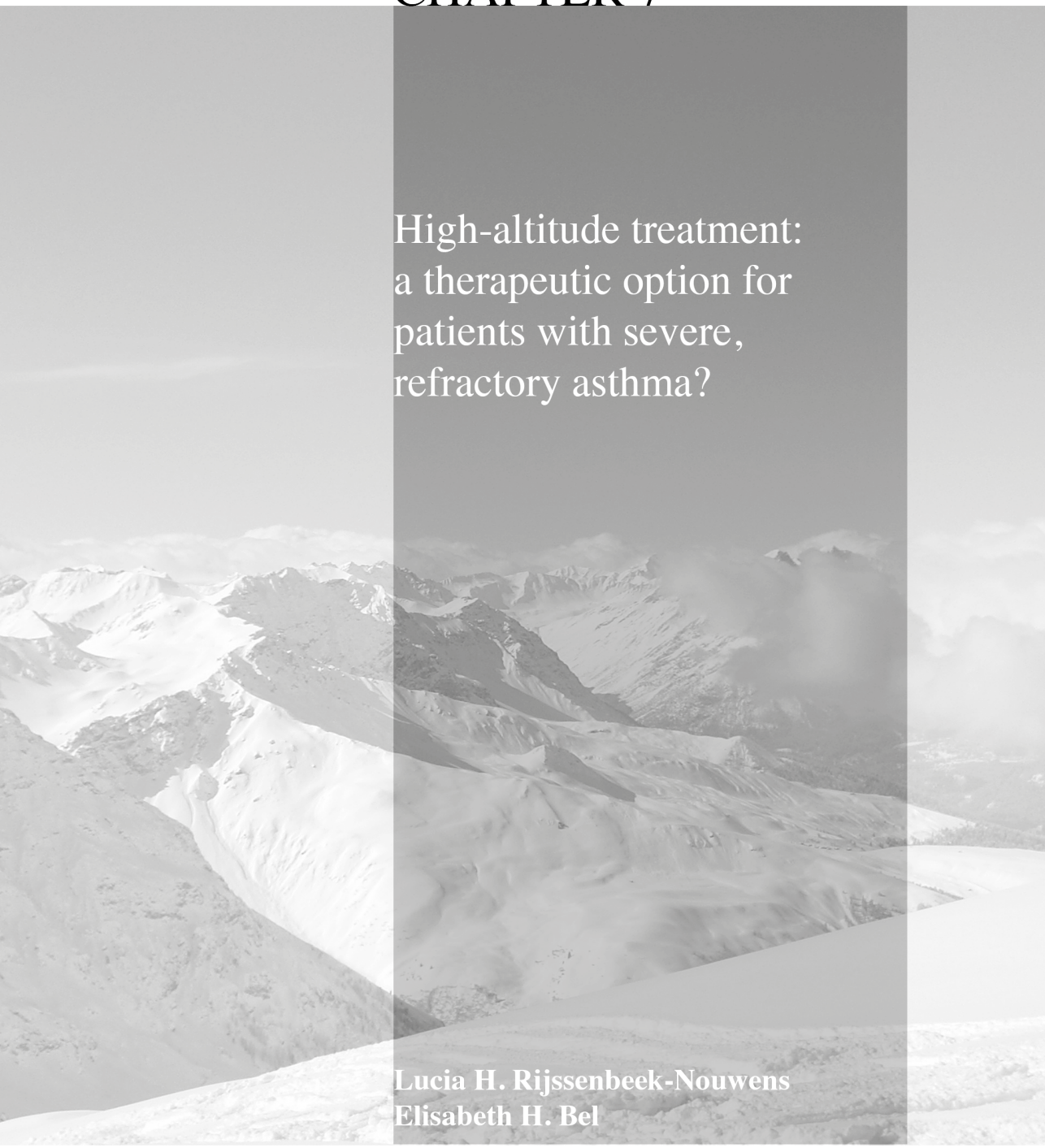
CHAPTER 7



High-altitude treatment: a therapeutic option for patients with severe, refractory asthma?

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Abstract

High-altitude treatment has been applied for more than a century in the treatment of pulmonary diseases including asthma. Many uncontrolled and controlled studies have shown its beneficial effects in children and adolescents with house dust mite allergic asthma. A recent study also showed an improvement in markers of airway inflammation in adult patients with severe intrinsic asthma, suggesting that factors other than HDM avoidance may contribute to the beneficial influence of the high-altitude climate therapy on asthma.

The dry mountain climate not only has decreased levels of mite allergens but also decreased levels of pollens, fungal spores and air pollution, as well as high exposure to UV light with immunomodulatory and anti-inflammatory effects.

Treatments targeting environmental control have never been investigated systematically in severe asthma, which is surprising, as environmental factors have been recognized as important contributors to asthma severity for many years and more evidence has been accumulating ever since. Preliminary evidence shows the beneficial effects of high-altitude treatment in patients with severe refractory asthma on symptoms, lung function and oral corticosteroid requirement, irrespective of atopic status.

In this narrative review, we will discuss why high-altitude treatment might be a promising therapeutic option for patients who suffer from this disabling disease.

Introduction

High-altitude treatment has been applied for >100 years in the treatment of asthma. The high-altitude environment is characterized by dry, clean air, with reduced levels of house dust mites (HDM)[1], particulate matters[2] and moulds[3]. Many uncontrolled and controlled studies have shown the beneficial effects of high-altitude treatment in children and adolescents with HDM-allergic asthma[4]. A recent study also showed an improvement in markers of airway inflammation in adult patients with severe intrinsic asthma[5]. In the present review, we will provide a historical perspective of high-altitude treatment over the last century, evaluate the results of clinical trials up till now and explore the potential of high-altitude treatment for patients with severe, refractory asthma.

Historical perspective of high-altitude treatment for asthma

In the pre-antibiotic era, high-altitude environments, such as the Alps and the Dolomites in Europe, attracted many patients with tuberculosis, because 'consumptive patients did very well in this climate and were benefited by staying there during the winter' [6]. At the same time, patients with other respiratory conditions, including those with asthma, also went to the mountains. The first observations of the benefits of the mountain climate for patients with asthma were reported in 1879 [7]. The author wrote: 'Asthmatic persons are so capricious that each patient has to find out for himself; a given asthmatic may lose his asthma at Davos. Only young persons should try the experiment, and persons free from emphysema'. A few years later, Turban and Spengler [8] reported the positive influence on health of the alpine climate in 143 patients with asthma. They found that 68% of all asthmatics going to Davos, situated at 1600 m above sea level, became free from asthma attacks within 2 or 3 days, that 25% improved considerably within 2 or 3 weeks and that only 7% remained uninfluenced. The beneficial effect was ascribed to the 'thin air', to the 'protective', 'roborant' and 'radiant' effect of the mountain climate, and to the change in social and psychosocial milieu. Another explanation of the favorable effect of the mountain climate on asthma symptoms was provided by Stäubli [9], who attributed the beneficial effects of the mountain climate to the absence of harmful factors in the environment.

High altitude: a house dust mite-free environment

In search for the underlying mechanism, the relationship of asthma symptoms with altitude was studied systematically by Storm van Leeuwen et al.[10], who took patients stepwise from sea level to the Alps. His study showed that the improvement in patients' conditions started at an altitude of 1200 m and reached a maximum at 1600 m. The author speculated that the effect might be attributed to 'climate allergens'. For the final proof, he developed an allergen-free air chamber in order to obtain conditions nearly identical to high altitude in the Clinic for Allergic Diseases in Leiden, the Netherlands. Seventy-five per cent of 500 patients, who stayed overnight in these chambers, were completely cured within a few days. In his opinion, 'this shows without any doubt that the conception of the influence of climate allergens on the condition of asthmatics in various climates and at various heights is correct' [11].

More than 50 years later, Storm van Leeuwens work was continued by Voorhorst and colleagues. They suggested a house dust allergen to be the most plausible triggering factor in allergic patients with asthma and indicated the mite *Dermatophagoides pteronyssinus* as the main allergenic component of house dust [12]. Dust from houses in high-altitude moun-

tains appeared to contain fewer HDMs and less allergen than house dust from lower parts of Switzerland and from sea level[1]. Finally, Vervloet affirmed the effect of altitude on HDMs. In dust samples from different altitudes (900–1200–1400–1600 m), he showed that not only the concentration of mites in dust but also the levels of total and specific IgE in mite-allergic children varied inversely with altitude[13]. The extremely low-humidity levels, preventing the growth of allergen-producing HDMs, therefore seemed likely to contribute to the favorable climatic conditions at high altitude.

High altitude treatment in children with allergic asthma

The first observational studies on the effects of high-altitude treatment in children with HDM-allergic asthma were performed by Kerrebijn et al.[14]. He studied 31 children with oral steroid-dependent asthma who were sent to Davos for 3 months. In all patients, corticosteroids could be discontinued without untoward effects. In approximately half of the patients, re-institution of oral corticosteroids was not necessary until at least 6 months after the child's return home. Both pituitary–adrenal function and statural growth were improved while corticosteroid therapy was interrupted [14].

To test the effect of a HDM-free environment on airway hyper-responsiveness (AHR), he subsequently studied 20 allergic asthmatic children with a sensitization to HDM during 1 year of treatment in an asthma clinic in Davos. The results showed a remarkable clinical improvement and a progressive reduction in bronchial hyper-responsiveness (BHR)[15]. This effect of an HDM-free environment on BHR was confirmed by Platts-Mills et al.[16]. He studied nine HDM-sensitized asthmatic patients who lived in hospital rooms for 2 months or more. In all patients, symptoms and early morning peak flows improved. In seven patients, anti-asthma treatment could be reduced and five patients showed a progressive improvement in AHR[16].

In a pilot study in 1985, Boner et al.[17] reported clinical improvement in 23 children with severe asthma referred to a special school in Mirusina (1756 m), Italy. After a residency at high altitude of at least 3 months, all children improved to the extent that most regular therapy could be discontinued. Subsequently, the same group reported clinical improvement in 14 children with allergic bronchial asthma after an 8-month period at high altitude[18]. These children showed decreased bronchial lability, decreased requirement for asthma medications and discontinuation of oral corticosteroids.

Over the next 20 years, Boner and colleagues published the results of a series of studies in which they used the migration of HDM-allergic, asthmatic children from sea level to a

high-altitude environment and back again as a natural allergen exposure-avoidance challenge model[19–34]. By applying their model in small cohorts of 10–25 children, who acted as their own control, they obtained the following results. After a 3-month stay at high altitude, the asthmatic children showed a decline in peak expiratory flow (PEF) variability[22], and an improvement in airway responsiveness to methacholine[22], histamine[19,21] and exercise[21].

The early and late response to HDM challenge were diminished, as well as allergen-induced AHR[21], and sputum eosinophilia[33]. There was a decrease in serum total IgE and specific IgE to HDM[21], as well as a decrease in serum eosinophil cationic protein (ECP) and urine eosinophil protein X[20,25]. Also, the percentage of eosinophils and epithelial cells in induced sputum[24,27,29], as well as the level of exhaled nitric oxide[28,30–32] and the concentrations of *cys*-leukotrienes and 8-isoprostane in exhaled breath condensate[27] were reduced after a few months' stay at high altitude. Forced expiratory volume in 1 s (FEV_1) did not change in most studies, but measures of small airways function (FEF 25–75 and residual volume) improved [23,26,29], and there was a significant improvement in deep-breath-induced bronchodilatation [35].

All these studies convincingly showed that in children with HDM-allergic asthma, a stay at high altitude led to an improvement in symptoms, AHR to specific and nonspecific stimuli and markers of airway inflammation. Unfortunately, all these effects wore off as soon as the children returned to sea level, where the concentration of HDMs was higher than in the mountains[13]. Only if inhaled corticosteroids were administered as prophylaxis could the deterioration in airway responsiveness and inflammatory markers such as exhaled nitric oxide be prevented [31,36].

In the meantime, other groups performed similar experiments in children with asthma during allergen avoidance at high altitude. Simon et al.[37] studied 14 HDM-allergic asthmatic children and showed an improvement of lung function and reduction of peripheral blood eosinophils after 3 weeks at high altitude in Davos. Christie et al.[38] performed a randomized-controlled study in Dutch children who were staying at the Asthma Centre in Davos for at least 1 month, and returned home for a short period of 2 weeks. As compared with the children who remained in Davos, the children who returned from the Netherlands showed a significant decline in FEV_1, an increase in airway responsiveness to histamine, accompanied by a threefold increase in urinary leukotriene E_4 (LTE_4). Van Velzen et al.[39] investigated the effect of the mountain climate on airway inflammation in 16 children who were still symptomatic despite inhaled corticosteroids. After a 1-month stay in Davos, they found an improvement in PEF variability and airway responsiveness to

adenosine (but not methacholine), and a reduction in blood eosinophil counts and serum ECP. Benckhuijzen et al.[40] found similar results in HDM-allergic asthmatic children who remained uncontrolled despite the chronic use of inhaled corticosteroids and bronchodilators. After a 1-month stay at Davos, airway responsiveness to indirect stimuli (adenosine and exercise) was improved, whereas responsiveness to a direct stimulus (methacholine) was still unchanged. The authors concluded that adenosine and exercise challenge were more adequate markers of airway inflammation than AHR to methacholine.

Grootendorst et al.[41] performed a parallel controlled intervention study investigating the short- and long-term effects of high-altitude treatment in 18 children with HDM-allergic asthma, who were symptomatic despite high-dose inhalation steroids and long-acting β_2-2-agonists. They showed a significant improvement in quality of life (QOL), FEV_1, AHR to adenosine and histamine, and urinary markers of airway inflammation (EPX, LTE_4, 9α11β-PGF_2) compared with patients staying at sea level.

Thus, high-altitude treatment has a beneficial effect on QOL, AHR and markers of airway inflammation not only for children with mild-moderate HDM-allergic asthma but also for allergic children with more severe asthma who remain symptomatic despite treatment with high doses of inhaled corticosteroids and long-acting β_2-2-agonists.

High- altitude treatment: more than just mite-allergen avoidance?

Whether the climate at high altitude might also be beneficial for asthmatic patients with allergies other than HDM and for non-atopic patients with asthma has never been addressed systematically. However, two recent reports suggest a beneficial effect of a high-altitude climate in patients with asthma who were not allergic to HDM. The first report showed a significant reduction in the mean exhaled NO value in children after a 4–6-week inpatient rehabilitation programme in the Bavarian Alps (at 1200 m altitude), irrespective of concomitant atopic diseases or anti-asthmatic drugs[42]. The second report was even more intriguing, as it showed the beneficial effects of high-altitude treatment in adults with allergic and intrinsic moderate, severe and steroid-dependent asthma[5]. In 72 patients admitted to a high-altitude clinic in Davos, the authors observed a significant decrease in the level of exhaled nitric oxide in patients with allergic and intrinsic asthma within 3 weeks of high-altitude treatment. In their paper, the authors stated that ‘especially patients with severe asthma profit from high altitude climate therapy (…) and in most cases the dose of systemic glucocorticoids can be reduced under high altitude climate therapy conditions’. As patients with intrinsic

asthma showed similar reduction in airway inflammation as compared with patients with allergic asthma, the authors concluded that 'factors other than allergen avoidance (…) contribute to the beneficial influence of the high altitude climate therapy on asthma'.

The importance of environmental factors in severe asthma

Severe refractory asthma is a complex, challenging problem both in children[43] and in adults[44]. There is a major unmet need to find better treatments for patients with this disease[45]. To date, there are only a few treatment options available. Oral corticosteroids are effective in most patients, but far from optimal, due to their side-effects[46]. Targeted treatment with biologicals might be successful, but unfortunately, only in specific asthma phenotypes[47–51]. Treatments targeting environmental control have never been investigated systematically in severe asthma, which is surprising, as environmental factors have been recognized as important contributors to asthma severity for many years[52] and more evidence has been accumulating ever since[53–55].

Different environmental factors may contribute to airway inflammation in severe asthma, including perennial exposure to HDM allergen[56] and fungi[57], inadequate sunlight exposure leading to vitamin D deficiency[58] and air pollution[55].

House dust mites

Exposure to HDM undoubtedly contributes to the severity of asthma in sensitized patients [52,56,59]. Asthma has convincingly been shown to be more severe in sensitized patients who are exposed to higher HDM allergen levels and effective allergen avoidance is consequently recognized as an integral part of the overall management of the sensitized asthma patient[60]. However, environmental control is difficult. Even with a major reduction in allergen levels, it may take many months before the beneficial effect on symptoms, medication use, pulmonary function, non-specific and specific BHR and immunological parameters becomes fully apparent[61]. A systematic review showed that chemical and physical methods aimed at reducing exposure to HDM allergens are not effective[62]. Therefore, allergen avoidance measures have to be multifaceted[63]. This fits in with the observation that an individualized, home-based, comprehensive, environmental intervention, decreasing indoor allergens, results in reduced asthma-associated morbidity[64].

The high-altitude climate is one of the few natural HDM-free environments and may therefore be of interest for sensitized patients with severe allergic asthma.

Fungi

There is increasing evidence of a close association between fungal sensitization and asthma severity in adults and children [57,65,66]. One key aspect of fungi is that they not only have potent allergenic properties but they also have the ability to actively germinate, colonize and infect the respiratory tract, providing a chronic source of allergen exposure, and thus have a much greater impact on the severity of asthma[57]. Recently, it was shown that patients sensitized to A. fumigatus compared with non-sensitized patients with asthma had lower lung function, more bronchiectasis and more sputum neutrophils [67]. Indeed, severe asthma patients with fungal sensitization respond favorably to oral antifungal therapy, with a clinically relevant improvement in QOL and steroid requirement[68]. More importantly, symptoms of asthma and rhino-sinusitis have been shown to improve, and medication use to decline, following the removal of indoor mould, by lowering indoor humidity[69]. Alternatively, mould control, by insulation and use of moisture-impenetrable barriers, is effective in reducing self-reported wheeze, and hospital admissions for respiratory conditions[70]. Altogether, indoor exposure to perennial allergens, including HDM and fungi, is deleterious for asthma patients, and needs to be avoided. As both HDM and fungi grow under humid conditions, it seems rational for patients with severe asthma to search for a low-humidity environment [69,71].

Vitamin D deficiency due to limited exposure to sunlight

Vitamin D deficiency is highly prevalent in the general population, in particular among patients with chronic lung diseases. There is now accumulating evidence that vitamin D deficiency may contribute to the severity of asthma[58]. Vitamin D deficiency is associated with increased AHR[72], lower pulmonary functions[73], worse asthma control[74] and possibly steroid resistance[75–77]. A recent study demonstrated that vitamin D levels were inversely associated with the total IgE and eosinophil count[74]. Additionally, patients with higher vitamin D levels were associated with fewer hospitalizations and decreased need for anti-inflammatory medications[74]. Low vitamin D levels may promote bronchial smooth muscle proliferation and airway remodelling in asthma[78]. Recent evidence suggests that vitamin D deficiency might lead to greater occurrences of viral respiratory tract infections[79 80], and consequently, more asthma exacerbations[74].

Thus, vitamin D deficiency seems to be an important, as yet unrecognized, factor contributing to asthma control, severity and prognosis. Several controlled trials are now underway to investigate whether the administration of high doses of vitamin D_3 leads to improvement of severe asthma (http://www.ClinicalTrials.gov).

Air pollution

The health effects of air pollution have been subject to intense study in recent years. Air pollution is now considered to be a major environmental health issue[55]. Exposure to particulate matter and volatile organic compounds is associated with worse respiratory health[81], and an increased risk of hospitalizations and ICU admissions for asthma, especially in children[82,83]. Long-term exposure to relatively low levels of air pollution is associated with a higher prevalence of respiratory symptoms and a decline in lung function in adults[84,85]. Diesel exhaust triggers asthma symptoms and enhances airway inflammation in patients with asthma[86]. In a randomized crossover study, short-term exposure to diesel traffic in an urban roadside environment resulted in a significant decrease in lung function and an increase in inflammatory markers in sputum and exhaled breath condensate[87]. Nitrogen dioxide and ozone may exacerbate severe asthma and even cause death among patients with asthma[88]. Alternatively, reduction of air pollution exposure contributes to improved respiratory health in children[89] and attenuation of the rate of decline in lung function in healthy adults[90]. In children with asthma, 1 week at a summer camp in a less-polluted rural environment at a 1500 m altitude led to a rapid reduction in airway inflammation and an improvement of airway function[91].

Taken together, long- and short-term exposures to air pollution have adverse effects on lung function, respiratory symptoms and airway inflammation in children and adults, whereas reduction in air pollution exposure improves lung function and respiratory health.

High altitude: the ideal environment for patients with severe asthma

The climate at high altitude offers unique conditions for patients with asthma, in particular those with severe disease.

First, because of the low relative and absolute indoor and outdoor humidity, the mountain climate is not only free of HDMs but also relatively free of other airborne allergens that are associated with severe asthma including fungal spores and moulds [1,13,53,71]. Indeed, as a result of the dryness at high altitude, the number of Cladosporium spp. spores is 25–50% that of lower areas and Alternaria spores only 1–3%[3].

Patients with pollen allergies might also benefit from a mountain climate. Because the slopes are covered by snow for 6 months of the year, the pollen season is short, and clinically relevant pollen concentrations are only found for a few days per year (*Source*: Me-

teoschweiz). These low airborne allergen concentrations also offer additional possibilities for allergen testing in patients with severe allergic asthma, and for the initiation of immunotherapy under allergen-free or low allergen conditions.

Second, the high-altitude climate may have a direct physiological benefit because of the lower viscosity of the air and lower oxygen concentration. The decreased density of the air reduces respiratory resistances and increases inspiratory and expiratory flows, promoting full expansion of the lungs and decreasing lung resistance, which makes it easier to breathe[92]. This may also help to improve exercise capacity and physical fitness in patients with severe asthma.

Third, by moving to the mountains, the patients are literally moved away from psychological stress at home or at work. Psychological stress has been shown to enhance airway inflammation by modulating immune cell function through neural and hormonal pathways[93]. Chronic stress is associated with reduced responsiveness to corticosteroids[94] and causes asthma exacerbations in children[95]. Stress-reducing interventions have been shown to have beneficial effects on asthma severity[96] and contact with the natural mountain environment offers an effective way of achieving stress reduction. Of course, this is not unique for the mountains, but holds true for any relaxing environment far away from home.

Fourth, the Alps and Dolomites are well known for their abundance of sunshine. Exposure to UV light stimulates vitamin D photosynthesis in the skin and may modulate the immune system, thereby potentially reducing the severity of chronic diseases, such as asthma [58,97].

Fifth, the mountain outdoor climate in the Alps is far less polluted than the climate in other parts of Europe at sea level such as the Netherlands. For example, in 2005, the particulate matter (PM10) in the Alps was <10 $\mu g/m^3$, whereas it was 20–40 $\mu g/m^3$ in the Netherlands and >45 $\mu g/m^3$ is some parts of Northern Italy[2].

Finally, asthma clinics such as the ones in Davos, the Italian or the Bavarian supply structured, quality-controlled comprehensive tailor-made treatment plans for children and adults with severe asthma, which includes achievement of full asthma control, reduction of (oral) corticosteroids to the lowest effective level, exercise training, asthma education and self-management, and psychological support. For the above-mentioned reasons, such programmes are likely to lead to better outcomes than similar interventions at sea level, although this has to be confirmed by randomized-controlled trials.

Taken together, the high-altitude climate offers more than decreased levels of HDM allergens. It also offers decreased exposure to pollens, fungal spores and air pollution, as well as lower work of breathing, relief from stress and high UV-light exposure with a potential immunomodulatory effect. Because of these characteristics, it provides the ideal environ-

ment for patients with asthma, both atopic and non-atopic, and might be a valuable treatment option in patients with severe, refractory disease.

High altitude treatment for severe asthma: old concept, new evidence

Preliminary data investigating the effects of high-altitude treatment in adults with severe, refractory asthma show promising results. In allergic patients with or without sensitization to HDMs, and also in patients with intrinsic asthma, high-altitude treatment for 12 weeks in the asthma clinic in Davos leads to an improvement in asthma control, asthma-related QOL, pre- and post-bronchodilator FEV_1, fraction of exhaled NO, and total and specific IgE, with a concomitant reduction in the use of oral corticosteroids [98,99]. The improved asthma control creates the opportunity for the patients to optimize their exercise tolerance and improve physical fitness.

The next step will be to study the long-term benefits of this high-altitude treatment program in terms of asthma control, QOL and exacerbation rate. If patients with severe refractory asthma are able to maintain their physical fitness and asthma control at acceptable levels for prolonged periods of time without exacerbations or hospital admissions, periodic rehabilitation programs at high altitude would constitute an elegant treatment option for these compromised patients.

Future research perspectives

To date, there is a surprising lack of data on the beneficial effects of high-altitude treatment in adults with severe refractory asthma. Because patients with this serious disorder depend on drugs that either have serious side effects or are only effective in small subsets of patients, more research is urgently needed. Firstly, it has to be demonstrated in randomized controlled trials that the effect of high-altitude treatment is superior to a similar treatment program at sea level. This has never been done before. In all the published studies, patients were their own controls or were not randomized into treatment arms, which might have introduced a selection bias. Secondly, it has to be investigated whether the beneficial effects of high-altitude treatment differ between different phenotypes of severe asthma, and what characterizes the patients with the most favorable response. Thirdly, the environmental factors and inflammatory mechanisms that are associated with clinical and functional improvement as a result of high-altitude treatment should be explored in more detail, especially in patients without allergic sensitization. Finally, the relative potential of a high-altitude intervention in terms of costs, duration and sustainability as compared with current established and experimental treatments should be investigated.

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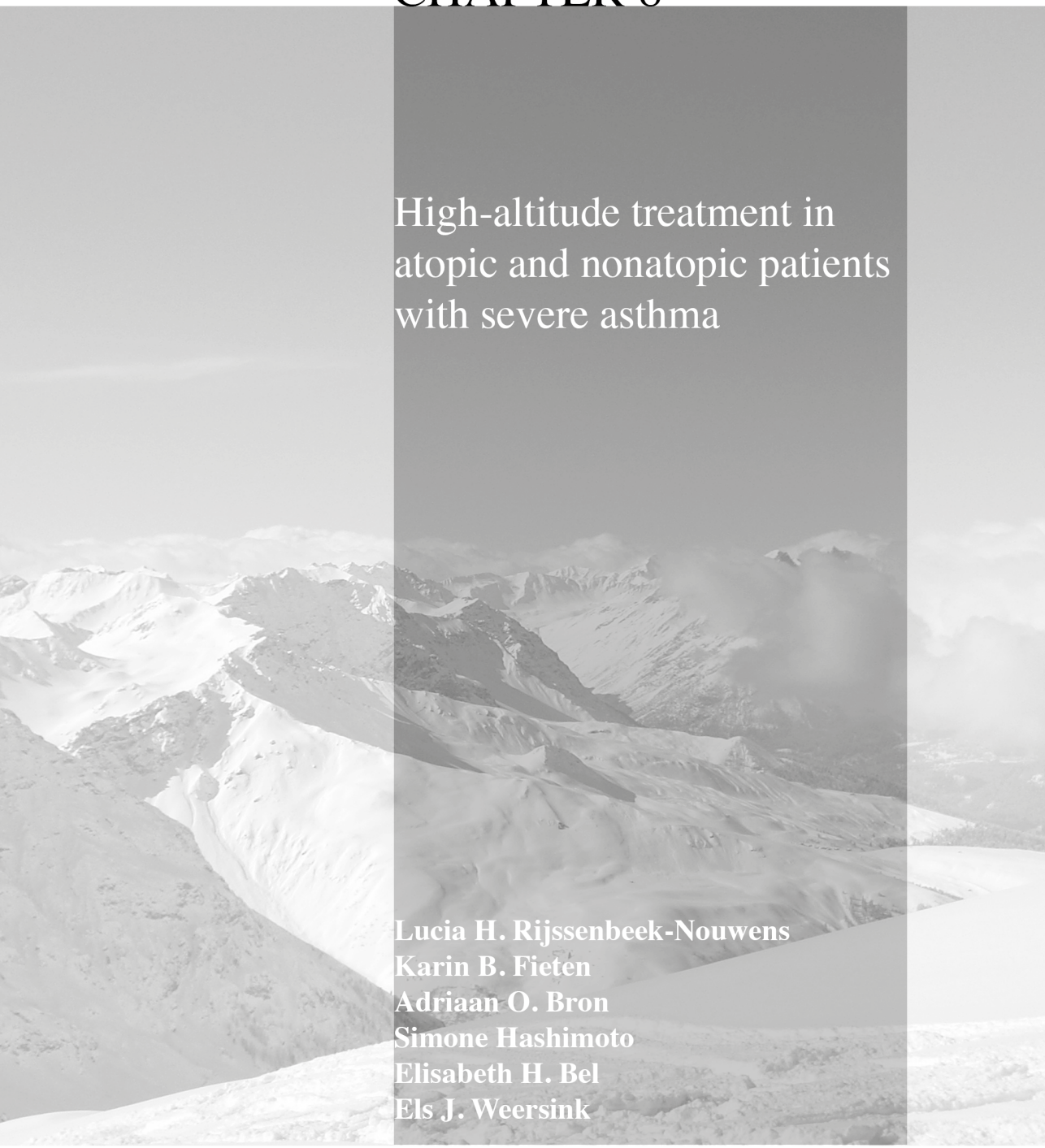
CHAPTER 8



High-altitude treatment in atopic and nonatopic patients with severe asthma

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Abstract

Background

The beneficial effects of high-altitude treatment in asthma have been attributed to allergen avoidance. Recent evidence shows that this treatment also improves airway inflammation in nonallergic patients. We hypothesised that high-altitude treatment is clinically equally effective in patients with severe refractory asthma, with or without allergic sensitisation.

Methods

In a prospective observational cohort study, 137 adults with severe refractory asthma (92 with allergic sensitisation), referred for high-altitude (1,600 m) treatment in Davos, Switzerland, were consecutively included. We measured asthma control (Asthma Control Questionnaire (ACQ)), asthma-related quality of life (Asthma-Related Quality of Life Questionnaire (AQLQ)), sino-nasal symptoms (Sino-Nasal Outcome Test (SNOT-20)), medication requirement, postbronchodilator (post-BD) forced expiratory volume in 1 s (FEV_1), 6-min walking distance (6MWD), total immunoglobulin (Ig)E, blood eosinophils and exhaled nitric oxide fraction (F_{eNO}) at admission and after 12 weeks.

Results

Sensitised and nonsensitised patients showed similar improvements in ACQ (-1.4 and -1.5, respectively; p=0.79), AQLQ (1.6 and 1.5, respectively; p=0.94), SNOT-20 (-0.7 and -0.5, respectively; p=0.18), post-BD FEV_1 (6.1% and 5.8% pred, respectively; p=0.87), 6MWD (+125 m and +147 m, respectively; p=0.43) and oral steroids (40% *versus* 44%, respectively; p=0.51). Sensitised patients showed a larger decrease in total IgE, blood eosinophils and F_{eNO}.

Conclusion

High-altitude treatment improves clinical and functional parameters, and decreases oral corticosteroid requirement in patients with severe refractory asthma, irrespective of allergic sensitisation.

Introduction

The majority of patients with mild-to-moderate asthma can be treated adequately with inhaled corticosteroids combined with long-acting bronchodilators[1]. However, this therapy is not sufficient to reach asthma control in patients with severe refractory asthma[2]. For these patients, there are only a few effective therapeutic options available, including systemic corticosteroids, which have serious adverse effects[3], and monoclonal antibodies against immunoglobulin (Ig)E, which are indicated only for patients with allergic asthma[4]. For nonatopic patients with severe asthma, however, there is an urgent need for better therapies[5].

High-altitude treatment has been applied for decades in patients with asthma, especially in children and adolescents with moderate-to-severe atopic disease[6–9]. The success of this treatment has long been attributed to the absence of house dust mite allergens at altitudes >1,600 m[10]. However, two recent studies, one in children and one in adults, have shown that high-altitude treatment also reduces airway inflammation in patients with allergies other than house dust mite, or no allergies at all [11,12]. This suggests that factors other than allergen avoidance contribute to the beneficial influence of high-altitude treatment, and that this treatment might be a valuable therapeutic option for patients with severe, nonatopic asthma.

The present prospective observational study was designed to test the hypothesis that high-altitude treatment is equally effective in severe asthmatic patients with or without house dust mite allergy and with or without any allergies. To that end, we compared the effects of 12 weeks of high-altitude treatment on clinical, physiological and inflammatory parameters in patients with severe refractory asthma with and without sensitisation to house dust mite or other aeroallergens, who were referred to the Dutch Asthma Centre Davos (Davos, Switzerland) for high-altitude treatment.

Methods

Patients

Between January 2008 and January 2010, all adult patients who were referred to the Dutch Asthma Centre Davos with a diagnosis of severe, refractory asthma according to American Thoracic Society (ATS) criteria[13] were asked to participate in the study. They all used high doses of inhaled corticosteroids (≥1,260 μg per day of beclomethasone or equivalent) or oral corticosteroids combined with long-acting bronchodilators for ≥1 yr. All patients were symptomatic and had had at least one severe exacerbation during the past year requiring a course of oral corticosteroids, or were receiving chronic oral corticosteroid therapy. All patients were either nonsmokers or ex-smokers. In order to exclude patients with smoking-related chronic obstructive pulmonary disease, patients with a smoking history >15 yrs had to show a reversibility in forced expiratory volume in 1 s (FEV_1) to short-acting β-agonist of >12% predicted. Before being referred for the high-altitude clinic inhalation technique, adherence to treatment and optimal avoidance of exposure to allergens and cigarette smoke was checked using a questionnaire completed by the referring pulmonologist. The study was approved by the Ethics Committee of the Academic Medical Centre of the University of Amsterdam (Amsterdam, the Netherlands). All patients gave their written informed consent. This study was registered at the Netherlands Trial Register, under NTR 1277.

Study design

We conducted a 12-week prospective observational cohort study in patients with severe, refractory asthma who were referred to the Dutch Asthma Centre Davos for high-altitude treatment in order to optimise their disease. Patients were assessed and evaluated according to a systematic protocol at entry and after a 12-week multidisciplinary comprehensive treatment.

High-altitude treatment: climate and specialised treatment

The high-altitude climate offers an environment with low levels of allergic and nonallergic bronchoconstricting stimuli. The multidisciplinary treatment at high altitude consists of a personalised, structured and comprehensive treatment plan aimed at achieving full asthma control and improving patient's physical condition with the lowest possible dose of asthma medication. The quintessence of the treatment is the daily supervised exercise training indoors and outdoors in the trigger free environment.

Questionnaires

All patients filled in standard questionnaires including questions about current symptoms, medical history, age at asthma onset, smoking habits and medication usage. The dose of

inhaled corticosteroids was expressed in equivalents of inhaled beclomethasone and the dose of oral corticosteroids in milligrammes of prednisolone equivalents.

The six-item Asthma Control Questionnaire (ACQ) was used to assess the level of asthma control[14]. Responses to each item are rated on a six-point scale. The mean of the six items in the ACQ between 0 (totally controlled) and 6 (severely uncontrolled) was used.

The Asthma Quality of Life Questionnaire, standardised version (AQLQ-S)[15] was used to measure asthma-related quality of life. The mean of the 32 items in the AQLQ between 1 (very poor quality of life) and 7 (best quality of life) was used.

The rhino-sinusitis health status was measured by the 20-question Sino-Nasal Outcome Test (SNOT-20); the possible range of the SNOT-20 score is 0–5, with a higher score indicating a greater rhinosinusitis-related health burden[16].

Pulmonary function

Pulmonary function was measured by spirometry. FEV1 was assessed before and after inhaled administration of 400 μg salbutamol and expressed as the % predicted value. 5% pred values were obtained from the report of Quanjer et al.17. 6-min walk tests were performed according to ATS guidelines18

Allergy tests

Total IgE in peripheral blood was assessed by fluroenzyme immunoassay (UniCAP®; Pharmacia & Upjohn, Uppsala, Sweden) and expressed in $kU \cdot L^{-1}$. Sensitisation to specific IgE was assessed with a panel of common aero-allergens (house dust mite, mixed grass and birch pollen, cat and dog dander, and *Aspergillus*) by UniCAP® and expressed in $kU \cdot L^{-1}$. Patients were classified as sensitised to house dust mite if IgE to house dust mite was >0.35 $kU \cdot L^{-1}$.

Markers of systemic and airway inflammation

Eosinophils in peripheral blood were measured by standard automated cell counter.

Exhaled nitric oxide fraction (F_{eNO}) was measured using a chemiluminescence analyser (Niox; Aerocrine AB, Solna, Sweden)[19].

Statistical analysis

Changes in clinical, functional and immunological parameters from admission to discharge were analysed by paired t-tests and Wilcoxon signed rank test for paired samples. Unpaired t-tests and Mann-Whitney were used to analyse the differences between groups. A p-value <0.05 was considered statistically significant. SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

Of 180 patients who were asked to participate in the study, four patients refused for personal reasons. 137 patients completed the 12-week follow-up period and were included in the analysis. The other 39 patients left Davos at an earlier time-point. There were no differences in baseline characteristics between patients who did and did not participate in the study (data not shown). Patient characteristics at baseline are shown in Table 1 for 68 house dust mite-sensitised and 69 non-house dust mite-sensitised patients. In Table 2 the characteristics of 92 patients with any sensitisation to common aeroallergens and 45 without sensitisation are shown. Changes from baseline in clinical, physiological and inflammatory parameters in patients with and without sensitisation to house dust mite are shown in table 3, and with and without sensitisation to any aeroallergen in Table 4.

Table 1 | Baseline characteristics of patients with and without house dust mite (HDM) sensitization

	HDM-sensitised patients	Non-HDM-sensitised patients	p-value
Subjects n	68	69	
Female	50 (73)	43 (63)	0.251
Age yrs	41.5±14.5	48±15.3	0.009
Sensitised for any inhaled allergen	68 (100)	24 (35)	<0.001
Ex-smokers	28 (40)	22 (32)	0.321
BMI kg·m−2	28.8±5.9	28.1±6.9	0.551
Age of asthma onset yrs	4 (0–45)	12 (1–63)	0.001
Asthma duration yrs	25 (2–71)	33 (1–65)	0.455

Data are presented as n (%), mean±sd or median (range), unless otherwise stated. HDM: house dust mite; BMI: body mass index.

Table 2 | Baseline characteristics of patients with and without any allergic sensitization

	Sensitised patients	Nonsensitised patients	p-value
Subjects n	92	45	
Females	50 (73)	35 (78)	0.08
Age yrs	44±15.8	48±14.2	0.124
Sensitised to HDM	68 (74)	0	<0.001
Ex-smokers	32 (35)	18 (40)	0.555
BMI kg·m−2	28.0±56.7	29.4±5.7	0.261
Age of asthma onset yrs	5 (0–58)	12 (1–63)	0.001
Asthma duration yrs	33 (1–71)	24 (3–66)	0.455

Data are presented as n (%), mean±sd or median (range), unless otherwise stated. HDM: house dust mite; BMI: body mass index.

After 12 weeks of high-altitude treatment, improvements in asthma control, asthma-related quality of life, sino-nasal symptoms, FEV_1, 6-min walking distance and total IgE were observed in patients with and without sensitisation to house dust mite, while the daily requirement for oral corticosteroids was decreased. 14 (48%) out of 29 patients sensitised to house dust mite and 15 (36%) out of 41 patients without house dust mite sensitisation could discontinue maintenance treatment with oral steroids completely. In the patients who could not discontinue oral corticosteroid treatment, the mean daily dose of prednisolone equivalent decreased from mean±sd 26.3±13.3 to 14.3±10.3 mg (p=0.006) in those sensitised to house dust mite, and from 29.2±24.0 to 14.4±8.8 mg (p=0.001) in the non-house dust mite-sensitised patients.

There was a decrease in peripheral blood eosinophils and exhaled nitric oxide in patients with house dust mite sensitisation, which was not observed in non-house dust mite-sensitised patients. The effects of high altitude did not differ between patients with or without sensitisation to house dust mite for all other parameters (Table 3).

Similar results were obtained when comparing the effects of high-altitude treatment between patients with or without sensitisation to any airborne allergens (Table 4 and Figures 1 and 2). Both allergic (n=92) and nonallergic (n=45) patients with severe asthma showed improvements in clinical and physiological parameters. However, improvements in total IgE levels, peripheral blood eosinophils and exhaled nitric oxide were observed only in patients with severe allergic asthma.

Table 3 | Values at baseline and after 12 weeks of high-altitude treatment in patients with and without house dust mite (HDM) sensitisation

	HDM-sensitised patients			Non-HDM-sensitised patients			Significance between groups p-value
	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	
Subjects n	68			69			
ACQ score[#]	3.0±1.0	1.6±1.2	<0.001	3.3±1.0	1.8±1.0	<0.001	0.965
AQLQ score[¶]	4.0±0.9	5.6±1.0	<0.001	3.8±0.9	5.3±1.1	<0.001	0.952
SNOT-20 score[+]	2.2±0.8	1.5±1.1	<0.001	2.2±0.76	1.6±1.0	<0.001	0.412
Patients on OCS	29 (43)	15 (22)	<0.001	41 (59)	26 (38)	<0.001	0.87
OCS mg·day^{-1}	0 (0–60)	0 (0–40)	<0.001	5.0 (0–110)	0 (0–40)	<0.001	0.668
ICS µg·day^{-1}	1600 (200–8000)	1600 (0–8000)	0.533	1600 (0–8000)	1600 (0–8000)	0.4	0.584
FEV_1 % pred	88.4±20.4	94.2±20.1	0.001	86.5±26.2	92.8±23.1	0.004	0.838
6MWD m 516±178 636±219 <0.001				430±182	575±197	<0.001	0.36
Total IgE kU·L^{-1}	376 (7–5000)	245 (6–4682)	0.003	94 (5–1781)	58 (5–1961)	0.039	0.211
Blood eosinophils per µL of blood	235 (0–1050)	210 (50–570)	0.033	200 (0–880)	200 (0–630)	0.207	0.025
F_{eNO} ppb	27.6 (5–209)	18.4 (3–70)	<0.001	16 (5–224)	16 (1–61)	0.058	0.033

Data are presented as mean±sd or median (range), unless otherwise stated. Total immunoglobulin (Ig)E and blood eosinophils at 12 weeks were measured in 43 HDM-sensitised and 36 non-HDM-sensitised patients. ACQ: Asthma Control Questionnaire score; AQLQ: Asthma Quality of Life Questionnaire score; SNOT-20: Sino-Nasal Outcome Test; OCS: oral corticosteroids; ICS: inhalation corticosteroids; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; 6MWD: 6-min walking distance; F_{eNO}: exhaled nitric oxide fraction. [#]: 0–6, where 0=well controlled; [¶]: 1–7, where 7=best quality of life; [+]: 0–5, where 0=no complaints.

Table 4 | Values at baseline and after 12 weeks of high-altitude treatment in patients with and without any allergic sensitisation

	Sensitised patients			Nonsensitised patients			Significance between groups p-value
	Baseline	12 weeks	p-value	Baseline	12 weeks	p-value	
Subjects n	92			45			
ACQ score[#]	3.1±1.1	1.7±1.2	<0.001	3.3±1.0	1.8±1.0	<0.001	0.795
AQLQ score[¶]	4.0±1.0	5.6±1.0	<0.001	3.8±1.0	5.3±1.2	<0.001	0.939
SNOT-20 score[+]	2.2±0.8	1.5±0.9	<0.001	2.2±0.8	1.7±1.1	<0.001	0.184
Patients taking OCS	45 (49)	27 (29)	<0.001	25 (56)	14 (31)	<0.001	0.515
OCS mg·day^{-1}	0 (0–110)	0 (0–40)	<0.001	5 (0–75)	0 (0–40)	<0.001	0.568
ICS µg·day^{-1}	1600 (200–8000)	1600 (0–8000)	0.295	1600 (0–7400)	1600 (0–8000)	0.136	0.62
FEV_1 % pred	86.9±22.0	93±20.7	<0.001	88.6±26.1	94.4±23.5	0.019	0.87
6MWD	514±182	639±220	<0.001	397±164	544±174	<0.001	0.429
Total IgE kU·L^{-1}	369 (7–5000)	224 (6–4682)	0	51 (5–765)	40 (5–283)	0.55	0.044
Blood eosinophils per µL of blood	250 (0–1050)	220 (50–570)	0.022	120 (10–560)	130 (80–630)	0.037	0.005
F_{eNO} ppb	27 (5–224)	18 (1–70)	<0.001	15 (5–75)	16 (6–52)	0.343	0.009

Data are presented as mean±sd, n (%) or median (range), unless otherwise stated. Total immunoglobulin (Ig) E and blood eosinophils at 12 weeks were measured only in 59 sensitised and 20 nonsensitised patients. ACQ: Asthma Control Questionnaire score; AQLQ: Asthma Quality of Life Questionnaire score; SNOT-20: Sino-Nasal Outcome Test; OCS: oral corticosteroids; ICS: inhalation corticosteroids; FEV1: forced expiratory volume in 1 s; % pred: % predicted; 6MWD: 6-min walking distance; F_{eNO}: exhaled nitric oxide fraction. [#]: 0–6, where 0=well controlled; [¶]: 1–7, where 7=best quality of life; [+]: 0–5, where 0=no complaints.

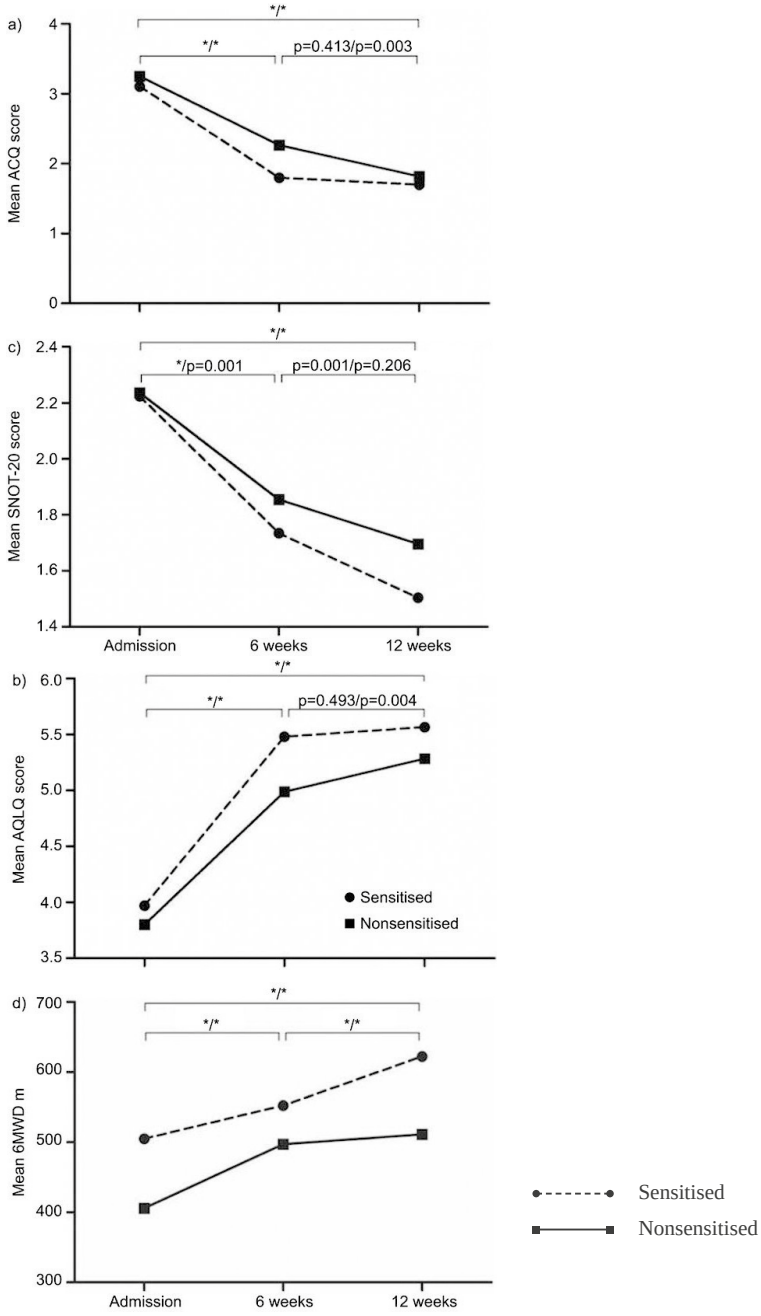

Figure 1 | The mean a) Asthma Control Questionnaire (ACQ) score, b) Asthma-related Quality of Life Questionnaire (AQLQ) score, c) Sino-Nasal Outcome Test (SNOT-20) score and d) 6-min walking distance (6MWD) on at admission, and after 6 and 12 weeks of high-altitude treatment in patients with (n=92) and without sensitisation to any allergen (n= 45). *: p<0.05. */*: p-values for patientswith/without sensitisation to any allergen.

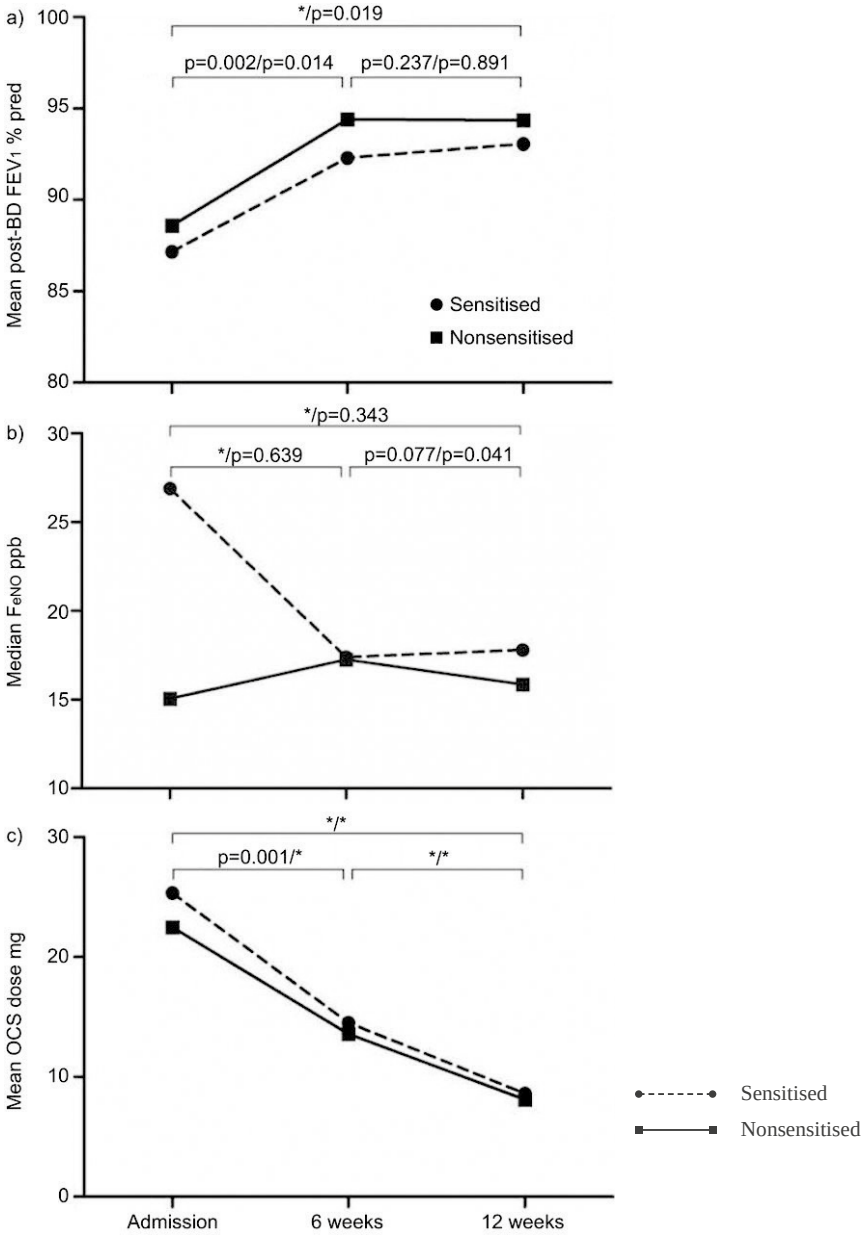

Figure 2 | The mean a) forced expiratory volume in 1 s (FEV_1), b) exhaled nitric oxide fraction (F_{eNO}) and c) oral corticosteroid (OCS) dose at the start of the study, and after 6 and 12 weeks of high-altitude treatment in patients with (n=92) and without sensitisation to any allergen (n=45). OCS dose was assessed only in patients on maintenance oral corticosteroid treatment at the start of the study (n=45/25). % pred: % predicted; post-BD: postbronchodilator. *: p<0.05.*/*: p-values for patients with/without sensitisation to any allergen.

Discussion

This study shows that patients with severe refractory asthma benefit from high-altitude treatment irrespective of sensitisation to house dust mite, or any common aero-allergen. The beneficial effect in clinical and functional parameters coincides with a decrease in oral corticosteroid requirement. Asthma symptoms, asthma-related quality of life, rhino-sinusitis symptoms, lung function and exercise performance improve to a similar extent in sensitised and nonsensitised patients, whereas total IgE, peripheral blood eosinophils and exhaled nitric oxide decrease only in sensitised patients. These findings suggest that high-altitude treatment is a valuable treatment option not only for patients with house dust mite allergic asthma, but also for patients with severe, refractory, nonallergic or "intrinsic" asthma.

This is the first study showing improvements in clinical and physiological parameters of high-altitude treatment in adults with severe, refractory asthma who are not sensitised to house dust mite. A large number of studies have shown beneficial effects of high-altitude treatment on asthma control, asthma-related quality of life, airway hyperresponsiveness and markers of inflammation in children and adolescents with house dust mite allergic, moderate-to-severe asthma[6–9, 20, 21]. Two studies have investigated the effects of high-altitude treatment on markers of airway inflammation and observed similar improvement in F_{eNO} in allergic and nonallergic patients, but in these studies, the effects on upper and lower airway symptoms, lung function, exercise capacity or medication requirement were not systematically addressed[11, 12].

Our study is unique in that it systematically evaluated the effects of high-altitude treatment in a large cohort of well-described patients with severe refractory asthma, and showed that beneficial effects occur irrespective of sensitisation to airborne allergens.

In our study, the treatment program was adjusted to the individual needs and capabilities of the patients. Theoretically, this might have introduced a treatment bias. However, the essence of the treatment, being the change in environmental exposure from a polluted, industrialised environment at sea level to the low-trigger environment at high altitude, was similar for both allergic and nonallergic patients. Moreover, there were no specific treatment adjustments related to the presence or absence of allergic sensitisation. Therefore, we do not believe that differences in treatments can explain the results of the present study.

It can also be argued that any individual, even without asthma, might benefit from a stay in the mountain climate. This might be true, but our patients had objective improvements in asthma symptoms, lung function and inflammatory parameters, as well as large im-

provements in exercise capacity and decreases in oral corticosteroid requirement, suggesting that high-altitude climate is particularly beneficial for patients with severe respiratory diseases. The improvements were the more striking since the patients in our study were referred to the high-altitude clinic because of long standing very severe, poorly controlled, refractory asthma by pulmonologists who are specialised in asthma care and working in academic hospitals or tertiary referral centres in the Netherlands. Clearly, decrease of exposure to allergens was not the only reason for the beneficial effect, given the similar improvement in sensitised and nonsensitised patients.

How can we explain the beneficial effects of high-altitude treatment in nonsensitised patients with severe asthma? Several factors might play a role[22]. First, the mountain outdoor climate in the Alps not only has very low levels of house dust mite, fungal spores and pollens[23], but is also far less polluted than the climate in other parts of Europe at sea level, such as the Netherlands[10, 24–26]. Secondly, the high-altitude climate may have a direct physiological benefit because of the lower viscosity of the air and lower oxygen pressure. The decreased density of the air reduces respiratory resistances and increases inspiratory and expiratory flows, promoting full expansion of the lungs and decreasing lung resistance, which makes it easier to breathe. This effect may be comparable with that of other low density gases, such as heliox, which have been applied successfully in patients with acute severe asthma[27]. Thirdly, by moving to the mountains, the patients are moved away from psychological stress at home or at work[28]. Psychological stress has been shown to enhance airway inflammation by modulating immune cell function through neural and hormonal pathways[29]. Finally, the Alps are well known for their abundance of sunshine. Exposure to ultraviolet light stimulates vitamin D photosynthesis in the skin and may modulate the immune system, thereby potentially reducing the severity of chronic diseases, such as asthma[30].

Because of all the above qualities, the low-trigger climate at high altitude provides the ideal environment for all patients with severe refractory asthma, whether sensitised or nonsensitised to house dust mites or common inhalation allergens.

The results of our study have clinical implications. As the clinical benefits of high-altitude treatment are similar in sensitised and nonsensitised patients, there is no reason to restrict this treatment to children and adolescents with atopic asthma and predominant house dust mite allergy[31]. Because of its beneficial effects on asthma control, exercise capacity and corticosteroid requirement, it should be offered to all patients with severe refractory asthma, including middle-aged and older adults with intrinsic disease[32]. The favourable climate at high altitude provides ideal circumstances to participate in pulmonary rehabilita-

tion programs and to improve exercise capacity and physical fitness for prolonged periods of time. Multidisciplinary, tailor-made treatment programs, such as the one offered by the Dutch Asthma Centre Davos, are likely to lead to better outcomes than similar interventions at sea level, although this has to be confirmed by randomised controlled trials[33].

In conclusion, we have shown that high-altitude treatment is a valuable treatment option for patients with severe refractory asthma, both for patients who are sensitised and not sensitised to airborne allergens. It significantly improves symptoms of the upper and lower airways, asthma-related quality of life, lung function and exercise capacity with a simultaneous reduction in the requirement for oral corticosteroids or even discontinuation of these drugs. High-altitude treatment is one of the very few efficacious treatments for patients with severe refractory asthma, and has no adverse effects. It is probably the best therapeutic option for patients with severe nonatopic asthma, for whom there is no treatment available other than systemic corticosteroids to control their disease.

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CHAPTER 9

Summary of the studies

Summary of the studies

Although total control of asthma is the ultimate goal of asthma treatment [1], the majority of asthma patients do not have their asthma under control at all. In uncontrolled asthma the search for factors related to the high symptom burden and/ or on-going inflammation is necessary in order to provide adequate treatment [2-4]. Moreover, to prevent future loss of asthma control, we need to identify factors contributing to loss of control.

The studies described in this thesis focused on some important patient related and environmental factors that may negatively influence asthma control.

- To examine patient related factors we performed an observational study of adherence to medication (*chapter 2*) and explored the usefulness of a health status instrument in disentangling the complexity of uncontrolled asthma (*chapter 3*).
- To elucidate the role of environmental related factors, we carried out a randomized double blind placebo controlled study of a house dust mite avoidance intervention (*chapters 4, 5 and 6*).
- To evaluate the effect of the combination of patient specific treatment and a low trigger environment, a prospective observational study was carried out in patients with uncontrolled asthma referred to the high altitude Merem Dutch Asthma centre in Davos (*chapter 7 and 8*).

Patient related factors

Non-adherence in relation to asthma control

The aim of the study in *chapter 2* was to investigate 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. Furthermore we compared adherence rates amongst patients with controlled and uncontrolled asthma.

Using the registration database of 47 community pharmacies all patients prescribed high dose inhaled steroids (ICS) or low dose ICS combined with oral steroids were identified and asked to complete a questionnaire on diagnosis, subject demographics, smoking history, health care utilisation and asthma control (ACQ). Sixty per cent of 754 patients with asthma had uncontrolled asthma (ACQ>1.5 or >2 exacerbations past year). The majority (75%) of all patients with controlled and uncontrolled asthma were non-adherent to ICS. Interestingly, the adherence rates were lower in patients with controlled asthma as compared to those with uncontrolled asthma.

Health status assessment in difficult to control asthma

In *chapter 3* we studied the usefulness of the Nijmegen Clinical Screening Instrument (NCSI) in measuring health status in patients with uncontrolled asthma. These patients experience problems in different domains of their health status, and identification of these problems may provide insight in factors contributing to coping and loss of control of asthma.

The NCSI was developed and validated for use in clinical care of patients with COPD, with the aim to provide a detailed picture of patient's symptoms, physiologic functioning, functional impairment and quality of life. We hypothesized that the NCSI can also be of value in patients with asthma. Therefore, in *chapter 3* we compared the NCSI with the ACQ and AQLQ in a cohort of 167 patients with uncontrolled asthma.

All sub-domains of the NCSI proved to be relevant, moreover high proportions of patients scored serious problems on five or more NCSI sub-domains. Heterogeneity was found on the number and on the combination of sub-domains on which patients reported severe problems.

The internal consistency for all sub-domains of the ACQ, AQLQ and NCSI was good. The NCSI questionnaire part measures eight aspects of health status, whereas the AQLQ measures four distinct aspects of health status. Inter-correlations between most of the NCSI sub-domains were moderate to absent between symptoms, physiological functioning, behavioural impairment and quality of life, representing conceptually distinct aspects of the patient's health status.

This study showed that the NCSI is of value in patients with uncontrolled asthma. The NCSI measured more aspects of health status than the ACQ and AQLQ, in particular airflow, body composition, general and health-related quality of life, satisfaction with relations, fatigue and behaviour impairment.

The PatientProfileChart (*chapter 3,* Figure 1) provides a detailed and comprehensive picture of the clinical and physiologic functioning, functional impairment and quality of life of the patient. This picture determines patient characteristics and assesses the relation between different domains of health status and therefore identifies coping patterns that may aggravate, complicate and influence control of asthma.

Environmental exposure related factors

Allergen avoidance and asthma control

In *chapter 4* we focused on avoidance of house dust mites, which are major environmental trigger factors for asthma. We studied the long-term effect of anti-allergic mattress covers versus placebo covers on asthma control in 30 patients with moderate to severe asthma sensitized to HDM. The use of covers was associated with a significant reduction in the concentration of HDM allergens. However, no change in asthma control and quality of life was measured between the actively treated group and the placebo group. We concluded that this mono-intervention of effective avoidance of one allergen is not effective in improving asthma control.

To investigate the underlying mechanism of allergen avoidance, we studied allergen specific parameters, described in *chapter 5*. Bronchial reaction to bronchial challenges with histamine and HDM, intra-dermal challenges with HDM and eosinophils in peripheral blood in 27 patients with moderate to severe HDM allergic asthma were measured before and after one year use of allergen impermeable mattress covers. A significant increase in HDM-induced bronchial early-reaction and peripheral blood eosinophils were measured in the placebo group, without significant change in the actively treated group, suggesting some protective effect of long-term allergen reduction against further increase in airway allergen sensitivity and inflammation.

As we summarized in *chapter 6*, a prerequisite of allergen avoidance is an efficient reduction of allergen exposure. When one realizes that in quite a few earlier studies the allergen load could not be reduced at all, it is not surprising that a Cochrane Review [5] showed that the use of anti-allergic mattress covers as single intervention in allergic asthma was of no clinical benefit. Furthermore, the environment accommodates many more triggers, so a single intervention will be of limited value.

Patient and environmental related factors combined

High altitude treatment and asthma control

In *chapter 7*, we reviewed the effects of high altitude treatment in patients with respiratory diseases. We summarize the studies exploring the features of the mountain environment and the effects of high altitude treatment in patients with uncontrolled asthma.

The high altitude environment in Davos at 1600 meter above sea level is characterized by very low humidity with greatly reduced levels of HDM, pollen and fungal spores. The mountain environment is far less polluted than industrialised urban environments and offers high UV-light exposure with potential immuno-modulatory effects.

Studies in the mountain climate of Davos and Misurina (Italy) have confirmed the beneficial effects of high altitude treatment on asthma control, on the need for oral corticosteroids, bronchial hyper-responsiveness and markers of inflammation in children and adults with uncontrolled HDM allergic asthma.

As the high altitude offers a low trigger environment, with little air pollution, we investigated whether high altitude treatment was also effective in patients without allergy. In *chapter 8* the effects of 12 weeks high altitude treatment in 137 patients with severe uncontrolled asthma are reported. Allergic and nonallergic patients showed similar and significant improvements in asthma control, quality of life, upper airways symptoms, lung function and exercise tolerance. Almost half of the patients sensitised to HDM and one third of the non-sensitised patients could discontinue maintenance oral steroids, while the other patients could diminish their oral steroid dose considerably. Based on these results we conclude that in patients with uncontrolled asthma with or without allergic sensitisation, high altitude treatment improves asthma control and increases the possibilities to live a normal life without limitations, with no or a lower dose of oral steroids.

Conclusions of the thesis

1. In a large cohort of patients with asthma who were prescribed high dose inhaled corticosteroids in primary and secondary care the majority (75%) of patients was poorly adherent to inhaled corticosteroids, irrespective of asthma control (*chapter 2*).

2. In this large cohort 60 % of the patients with asthma had uncontrolled asthma despite the prescription of high dose inhaled corticosteroids (*chapter 2*).

3. The Nijmegen Clinical Screening Instrument (NCSI), which has been developed for patients with COPD can also be used, and is a valuable instrument for the evaluation of patients with uncontrolled asthma (*chapter 3*).

4. Measurement of clinical, physiological and psychosocial domains by the NCSI provides a comprehensive spectrum of patient characteristics and identifies factors and patterns that may aggravate, complicate and influence control of asthma *(chapter 3*).

5. House dust mite (HDM) impermeable mattress covers reduce significantly the concentration of HDM allergens on the mattress (*chapter 4*).

6. The mono-intervention of avoiding HDM allergen exposure by mattress covers during one year is not effective in improving asthma control in patients with moderate to severe HDM allergic asthma (*chapter 4*).

7. During persistent long-term exposure to HDM allergens an increase in airway allergen sensitivity and inflammation was seen in patients with moderate to severe HDM allergic asthma (*chapter 5*).

8. An efficient and clinical relevant reduction of allergen exposure is prerequisite for allergen avoidance. The use of mono-interventions in allergic asthma is not enough to improve control in patients with allergic asthma (*chapter 6*).

9. High altitude treatment combines patient specific treatment with an optimal trigger free environment (*chapter 7).*

10. Allergic and non allergic patients with uncontrolled asthma show similar and significant improvements in asthma control, quality of life, upper airways symptoms, lung function and exercise tolerance while stopping or diminishing oral steroids during high altitude treatment in the Merem Dutch Asthmacentre Davos (*chapter 8*).

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CHAPTER 10

General discussion

General Discussion

Control of asthma is the goal of asthma treatment. However, it is largely unknown why controlling asthma remains difficult in many patients. For this reason we explored in this thesis patient and environmental related factors affecting asthma control.

Patient related factors

Non-adherence to medication in relation to asthma control

In *chapter 2* we showed that poor adherence is highly prevalent in a large cohort of patients with asthma. Our results extend previous results in specialised care and indicate that adherence is a problem in the majority of patients with asthma[1].

Remarkably, contrary to what we expected, patients with controlled asthma had more often low prescription fillings compared to patients with uncontrolled asthma, who generally showed overuse of prescribed dosage of medication. This suggests that patients did not feel the urge to continue their inhaled medication in controlled asthma and started using more medication when their asthma becomes uncontrolled. Thus, non-adherence seems not to be the important factor of uncontrolled asthma. Intervention studies aimed at improving adherence show good asthma control only in a minority of the patients[2]. Also we found no relation between non-adherence and asthma control. Remarkable, uncontrolled asthma leads to more use of medication, and therefore it is likely that more and other factors are contributing to loss of asthma control.

Guidelines stress the importance of asthma self-management for adequate coping strategies in asthma [3]. Self-management programs require patients to take substantial responsibility over their own health and unpredictable disease and have demonstrated to improve control of asthma [4,5]. Effective asthma self-management behaviour includes optimal adherence, adequate inhalation technique and self-monitoring with recognition of symptoms and changes in asthma control in order to adjust medication according to a personalized action plan [6,7]. Moreover the patient has to develop personalized and effective coping strategies for managing the physical and psychological consequences and life style changes inherent to uncontrolled asthma [8]. Taking the complexity of all these self-management and coping tasks into account, it is not surprising that personal and psychological factors will be very important in asthma control[9].

Health status measurement in relation to asthma control

In poorly controlled asthma numerous patient related factors interact with the disease, resulting in the patient experienced health status. How can we disentangle this complexity? Control of asthma concerns symptoms and other domains of health status, such as activity level and quality of life [4]. On the one hand uncontrolled asthma has an impressive impact on different domains of health status [10], on the other hand psychological factors and affected health status may influence control of asthma. Therefore, when control of asthma is difficult to achieve, it is necessary to investigate the different domains of health status to elucidate the complexity of the experienced illness [11].

In *chapter 3* we showed the applicability of the NCSI in asthma control assessment by identifying the clinical, physiological, functional and psychosocial domains of health status. The NCSI provides a detailed picture of health status and patient characteristics, allowing quick identification of problem areas and discrepancies between the different sub-domains, potentially contributing to loss of asthma control.

Measuring clinical, physiological and inflammatory markers of health status is essential to clarify a specific phenotype of asthma [12-14]. The NCSI adds the functional and psychosocial factors to this process providing a more comprehensive picture of the patient. Ideally, the NCSI should be supplemented with measurements of airway inflammation as FeNO and sputum eosinophils. This is possible, because the NCSI is a dynamic instrument, to which the designers can make additions. The NCSI is the first instrument that instantly visualizes the different subdomains of health status on a PatientProfileChart (*chapter 3*, Figure 1), elucidating discordances that can be addressed in the treatment of patients with un controlled asthma in order to achieve control of asthma [11].

In "discordant" asthma phenotypes, as described by Haldar and colleagues, the aetiology of symptoms was estimated to be multifactorial and not closely related to the underlying eosinophilic airway inflammation [12]. This multifactorial aetiology may point in the direction of psychosocial factors influencing symptom perception, factors that need to be explored in uncontrolled asthma. This fit in with our findings of high proportions of patients experiencing serious problems in different subdomains of the NCSI in *chapter 3*. Recognition of the differences between the patient subjective experience of symptoms, the so called "illness", and the objective parameters of the pathological process, the "disease", offers a rational basis for phenotype assessment and effective personalized treatment [15-17].

The experience of symptoms is influenced by emotions and acquired response tendencies [18-19]. As was observed in the cluster analysis of Haldar, patients may fail to perceive serious airway obstruction or suffer from breathlessness without objective obstruction.

These extremes in symptom perception are associated with (near) fatal asthma and excessive use of medication, respectively. The NCSI may be useful in the major challenge of exploring the multifactorial aetiology of the clinical presentation and experienced health status of the patient with difficult to control asthma.

Environmental exposure related factors

Allergen avoidance and asthma control

In *chapter 4*, we showed that long-term allergen avoidance by mono-intervention with HDM allergen impermeable mattress covers did not result in improving asthma control in patients with moderate to severe HDM allergic asthma. The results of our study reinforced those from previous studies in patients with mild asthma in which significant and clinical relevant reductions in exposure to HDM in beds did not result in improved control of asthma [20-22]. Similarly, failure of clinical effectiveness of anti-allergic covers was reported in patients with allergic rhinitis [23] and atopic dermatitis [24].

Do we have to conclude that HDM allergen avoidance is useless?

Because of the disappointing results of these mono-intervention studies, the confidence in the effectiveness of allergen avoidance gradually dwindled and clinicians lost interest in environmental factors [25]. Is this appropriate and justified? When allergen avoidance is neglected, this may pose a risk of future loss of asthma control. This is supported by our findings in *chapter 5* showing increased allergen sensitivity and inflammation in the patient group treated with placebo covers. Increasing parameters of inflammation were also observed during experimental repeated low-dose allergen exposure [26], underpinning the increased risk of loss of asthma control by persistent exposure to allergens. Moreover, mono-interventions directed at reduction of allergen exposure in bed do not take HDM exposure outside the bed into account, not to mention exposure to other allergens and non-allergic triggers.

Several studies provide evidence of the significant role of allergen sensitization and exposure in control of asthma. To summarize, sensitization to HDM and moulds is strongly associated with asthma severity in cross-sectional studies, while allergic sensitization and exposure to one or more allergens are associated with increased susceptibility to virus-induced asthma exacerbations, and the risk of being hospitalized [27-32]. Also indirect exposure to allergens, for example exposure to pet allergens in classrooms, can be the cause of decreased asthma control [33]. Exposure to allergens like HDM, pets and fungi play a

synergistic and critical role in asthma control and should be addressed as thoroughly as possible [25]. Therefore, our view is that allergen avoidance should be reconsidered as an important element of the treatment in difficult to control asthma.

Not only allergens, but also non-allergic triggers contribute to poor asthma control and need clinical attention. Exposure to air pollutants, tobacco smoke, strong odours, cleaning sprays, occupational agents and weather related factors are well known triggers to disturb asthma control [34-36]. Studies have shown that addressing individual sensitization and exposure to allergic and non-allergic triggers by multifaceted interventions leads to better outcomes than mono-interventions [37-40]. In line with these studies we showed in *chapter 8*, that a mountainous environment with low levels of allergens and air pollution may be an important factor in achieving asthma control in patients with uncontrolled asthma.

Patient and environmental related factors combined

High altitude treatment and asthma control

In *chapter 8*, we demonstrated that high altitude treatment is equally effective in patients with severe uncontrolled asthma irrespective of allergen sensitization. In both the allergic and non-allergic groups, the patients achieved a better asthma control and quality of life, both 3 times the minimal clinical important difference, with the ACQ just above the cut-off point of good control. We found a significant decrease in inflammation, measured by the exhaled nitric oxide fraction (Fe_{NO}) in the allergic group after high altitude treatment. The median of the baseline Fe_{NO} in the non-allergic group was within normal limits and did not change significantly. Despite the heterogeneous asthma phenotypes in this patient population, with the extremes of the symptom predominant and the inflammation predominant phenotype, beneficial effects were reached.

The equal effects in patients with and without allergy is not surprising, since hyper-responsiveness to non-specific triggers is a characteristic of all patients with asthma, and therefore, a low trigger environment is beneficial to every asthma patient [41]. The above mentioned results are unique. From published studies in similar groups of uncontrolled patients, it appears that novel pharmacological interventions, such as monoclonal antibodies against IgE (omalizumab) or Il-5 (mepolizumab) lead to a relatively small improvement in asthma-related quality of life, as compared to what was obtained by high altitude treatment in *chapter 8*, moreover, only in selected patients [42-44]. Other non-pharmacological treatments that were applied in this heterogeneous group of patients with severely difficult to control asthma (e.g. thermoplasty) also showed less impressive results [45].

How can we explain the beneficial effects of high altitude treatment?

Generally it is presumed that the low trigger exposure in the mountain climate contributes to better asthma control by offering the opportunity to down-regulate on-going inflammation, which can be seen as the opposite process of increasing allergen sensitivity and inflammation during persistent allergen exposure as we showed in *chapter 5*.

The pathogenic mechanisms of asthma include eosinophilic and non-eosinophilic pathways, potentially induced by allergens, viral infections and other non-allergic sensitizing triggers. Air pollutants and microbes may induce the release of epithelium-derived cytokines such as interleukin-5, which recruit eosinophils from the bone marrow and activate them, leading to airway inflammation and hyper-responsiveness [46]. Both pathways can develop independently of each other, but they can also coexist and interact [47].

Moreover, it is suggested that the coexistence of two or more inflammatory stimuli to the airways is a key factor leading to the development of more severe airway disease[48]. According to this "multiple hit hypothesis" removal of these triggering stimuli might reduce progression of the underlying disease and might help to restore control of asthma.

These mechanisms help us understand why the low trigger environment of Davos in both the allergic and non-allergic patients might reduce airway inflammation and hyper-reactivity and allow recovery of asthma control.

In addition to the trigger free mountain environment, assessment of the patient characteristics on the different domains of health status with the NCSI, enables the multi-disciplinary expert team to identify factors leading to loss of asthma control and to design a personalized, patient centred treatment plan. This combination of attention to patient related and environmental related factors resulted in significant improvements in asthma control in a heterogeneous group of patients with severe uncontrolled asthma, who had until then received maximal asthma treatment at sea level in the Netherlands (*chapter 8)* [49].

Strength and limitations of this thesis

This thesis is the first to explore patient and environmental exposure factors related to asthma control. Although we could not study all influencing factors, we covered important factors. We studied patients from primary, secondary and tertiary care, and investigated the effects of a single as well as of a comprehensive intervention. We showed that a single intervention of allergen avoidance was clinically not effective, whereas comprehensive trigger avoidance in combination with patient centred treatment showed remarkable results in a group of patients with uncontrolled asthma.

Not surprisingly, our studies had their limitations too.

First, due to limited resources, we did not have the opportunity to compare high altitude treatment with identical treatment at sea level. Such a comparison could have informed us better about the specific contribution of the mountain climate. This comparing study is designed recently and will inform us in future.

Second, our assumption that multidisciplinary expert treatment based on assessment of patient related factors is essential to improve control of asthma in patients with uncontrolled asthma, needs further investigation. A study design comparing patients receiving specialised high altitude treatment with those only staying at high altitude and not receiving any patient specific treatment could give us more information.

Third, we have no data yet on the long-term effects of high altitude treatment. Such studies are underway and results will be available in the near future.

Finally, we only obtained clinical evidence of down regulation of airway inflammation after high altitude treatment. We did not measure markers of airways inflammation in induced sputum samples or bronchial biopsies due to the lack of facilities in Davos.

Clinical implications

The studies presented in this thesis may have clinical implications. First, poor adherence to asthma medication should be kept in mind during treatment of patients with controlled and uncontrolled asthma at every clinical contact. The most practical and simple suggestion is to ask patients without prejudice how often they miss doses, and whether they have side effects of treatment. A good therapeutic relationship is the prerequisite to achieve concordance between patient and prescriber about the asthma medication which should be based on assessment of clinical, physiological, functional, inflammatory and psychological parameters. The NCSI, which is easy to handle and shows immediate results on the graphical PatientProfileChart can be a useful tool in daily practice.

Second, allergen avoidance interventions deserve innovative actions. Mono-interventions during night time leave the patient unprotected during the day and do not cover all exposures to triggering allergens. Therefore, this allergen avoidance intervention should not be abandoned, but should be accomplished with other multifaceted interventions not limited to the sleeping room.

When uncontrolled asthma is accompanied by increased markers of inflammation, the search for environmental trigger factors and the advice to avoid them as good as possible, remains an important part of asthma management in allergic and non-allergic patients. This should be addressed in the primary, secondary and tertiary care. Most likely, loss of asthma control is the result of a combination of several environmental and patient related factors, including exposure to allergic and non-allergic factors, individual susceptibility, coping abilities and illness perception. Patient related risk factors can be explored and addressed with the NCSI. Patient tailored advice, based on patient characteristics and exposure assessment should also include education and instruction on how to avoid risk factors.

Third, the combination of optimal environmental trigger control and patient profile based expert treatment in the high altitude Merem Dutch Asthmacentre Davos offers a relevant and clinically effective intervention. Patients who suffer significantly from persistent uncontrolled asthma, despite maximal treatment at sea level should be able to get the opportunity of this beneficial treatment.

Future research

First of all, explorative studies will be needed to determine why so many patients do not achieve control of their asthma, as this may have important consequences for adequate management strategies. Given the high burden of uncontrolled asthma, research on all potential factors influencing asthma control needs reinforcement. The focus of current asthma research is mainly on phenotyping and targeted treatment with biologicals. We recommend emphasizing non-pharmacological strategies to improve asthma control, in particular those affecting on-going inflammation on the one hand and high perceived illness burden on the other hand.

The full benefits of common asthma medication on asthma symptoms and airway inflammation cannot be obtained as long as levels of adherence are low. Therefore, more studies are needed using innovative approaches to assist patients in following medication prescriptions.

The validation of the asthma adjusted NCSI, with inflammatory domains, as well as exploration of its sensitivity to change with treatment needs further study.

Finally, the long-term effects, cost effectiveness and expedience of high altitude treatment for patients with uncontrolled asthma need to be studied. Currently, a study is being done on the long-term effects of treatment in which we monitor and support achieved control of asthma with web-based patient specific self-management information and plans. A randomized study comparing comprehensive tailor made treatment at sea level with that at high altitude will be worthwhile, although difficult to realize in this heterogeneous disabled patient population and is recently started.

Concluding remarks

In this thesis we focussed on non-pharmacological factors influencing asthma control. Patient related factors, such as adherence and psychological factors influencing coping mechanisms, as well as environmental related factors such as exposure to allergens and air pollution, play a role in loss of asthma control.

When asthma is poorly controlled the search for patient and environmental related factors is an important first step. Focussed intervention, based on these patient specific factors offers opportunities to achieve asthma control in patients with uncontrolled asthma. Based on the studies of this thesis we make the following statements related to achieving control of asthma:

1. Non-adherence is a frequent patient related factor in patients with controlled and uncontrolled asthma and should be explored and addressed at every patient contact.

2. Measurement of clinical, physiological, functional and psychological domains of health status by the NCSI provides a comprehensive picture of the patient characteristics and identifies factors and patterns that may influence control of asthma. The NCSI is useful in identifying the profile of the patient with uncontrolled asthma and in directing targeted treatment.

3. Addressing and removing environmental risk factors remains an important part of asthma treatment. Patient tailored advice should take care of allergic and non-allergic trigger factors and also include education.

4. Control of asthma can be achieved even in patients with severe allergic and non-allergic uncontrolled asthma, provided that treatment is based on patients' personal profile, guided by expert health professionals, and combined with optimal reduction of environmental factors.

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Nederlandse samenvatting

Nederlandse samenvatting, studies en algemene beschouwing

Astma

Astma is een chronische ontstekingsziekte van de luchtwegen, waarbij overgevoeligheid voor prikkels en vernauwing van de luchtwegen leiden tot symptomen van benauwdheid, piepen en hoesten. De ontsteking van de luchtwegen kan beschouwd worden als een veranderde, dan wel versterkte reactie van de luchtwegen op prikkelende omgevingsfactoren, die over het algemeen niet optreedt bij mensen zonder astma. Astma is een aandoening met verschillende verschijningsvormen, de zogenaamde fenotypen, die voortkomen uit een complexe interactie tussen genetische, patiënt gerelateerde en omgevingsfactoren.

Astmacontrole

Astma is helaas nog niet te genezen. Het doel van de behandeling van astma is derhalve het astma onder controle te krijgen en in de toekomst onder controle te houden Astmacontrole wordt gedefinieerd als de mate waarin de symptomen en signalen van astma zijn gereduceerd De mate van controle zegt iets over de effectiviteit van de behandeling.

Goede astmacontrole betekent voor de patiënt: zo weinig mogelijk klachten, geen behoefte aan noodmedicatie en een goede longfunctie. Een normaal activiteiten- en leefpatroon zonder beperkingen en een goede kwaliteit van leven horen hier bij. Als het astma goed onder controle is neemt de kans op toekomstige problemen, zoals astma-aanvallen, versneld verlies aan longfunctie en/of bijwerkingen van medicatie, af.

Slechte astmacontrole of ongecontroleerd astma daarentegen betekent dat een patiënt veel klachten heeft en noodmedicatie moet gebruiken naast de onderhoudsmedicatie. Astma dat niet onder controle is, veroorzaakt veelal beperkingen in het dagelijkse leven en kan een negatieve invloed hebben op de levenskwaliteit van de patiënt.

Astmacontrole kan gemeten worden met vragenlijsten, bijvoorbeeld de astmacontrole questionnaire (ACQ) of de astmacontrole test (ACT). Deze vragenlijsten bevatten vragen over astmasymptomen, verstoring van de nachtrust, beperkingen in activiteiten, behoefte aan noodmedicatie en de longfunctie. Aan de hand van de scores van de patiënt op deze vragenlijst kan de mate van astmacontrole worden geclassificeerd als goed, matig of slecht.

Astmacontrole en de ernst van astma

Astmacontrole heeft te maken met het beheersen van de ziekte symptomen en toekomstige risico's. De ernst van astma is een uiting van de activiteit van de onderliggende genetisch bepaalde ziekte. In de nieuwste internationale richtlijnen wordt de ernst van astma

gedefinieerd aan de hand van de hoeveelheid medicatie die nodig is om een goede astmacontrole te bereiken en te behouden. Zo wordt ernstig astma tegenwoordig gedefinieerd als astma, dat een hoog intensieve behandeling nodig heeft om te voorkomen dat het astma niet onder controle is of als astma dat ondanks deze intensieve behandeling ongecontroleerd blijft. Hoog intensief wordt gedefinieerd als hoge doseringen inhalatie steroïden en/of orale steroïden in onderhoud in combinatie met lang werkende luchtwegverwijders. De ernst van astma is een relatief stabiel gegeven, terwijl astmacontrole van dag tot dag kan veranderen als reactie op blootstelling aan omgevingsprikkels, virus infecties en medicatie gebruik.

Moeilijk te controleren astma

Met de ontwikkeling van krachtige inhalatie steroïden en langwerkende luchtwegverwijders is er een grote sprong voorwaarts gemaakt in de behandeling van astma. Met deze medicatie zou de meerderheid van de patiënten goed behandeld kunnen worden. Echter uit onderzoek blijkt dat bij meer dan de helft van de patiënten het astma niet goed onder controle te krijgen is. Bij een klein gedeelte van de patiënten is het zelfs heel moeilijk tot onmogelijk om, ondanks veel medicatie, het astma onder controle te krijgen en te houden, met als gevolg een hoge ziektelast voor de patiënt, een hoge zorgvraag voor de artsen en hoge maatschappelijke kosten. Waarom lukt dat niet?

Astmacontrole wordt niet alleen beïnvloed door medicatie maar wordt voor een belangrijk deel bepaald door patiënt en omgeving gerelateerde factoren. Bij ongecontroleerd astma is het van belang om de invloed van deze factoren helder te krijgen. Richtlijnen voor de diagnostiek en behandeling van ernstig en moeilijk te behandelen astma geven adviezen over een systematische aanpak van de verschillende factoren.

De in dit proefschrift beschreven studies richten zich op zowel patiënt gerelateerde factoren als omgevingsfactoren die van invloed op astmacontrole kunnen zijn. We hebben onderzocht in welke mate deze factoren een rol spelen en in hoeverre het zinvol is om bij de behandeling rekening te houden met deze factoren.

Patiënt gerelateerde factoren

Medicatiegebruik in relatie tot astmacontrole

Astma is een van de meest voorkomende chronische ziekten wereldwijd. Bij chronische ziekten is onzorgvuldig gebruik van preventieve onderhoudsmedicatie een veelvoorkomende oorzaak van het falen van behandeling. Onderhoudsmedicatie bij astma betekent regelmatig, dagelijks gebruik van inhalatie steroïden met als doel de ontsteking te onder-

drukken en zo het astma onder controle te houden. Omdat er nauwelijks iets bekend is over de zorgvuldigheid bij het gebruik van medicatie bij patiënten met astma in Nederland hebben we hier onderzoek naar gedaan *(hoofdstuk 2).* Aan de hand van receptregistraties van 47 apotheken hebben we patiënten geselecteerd die hoge doseringen inhalatie steroïden voorgeschreven kregen. Aan deze patiënten hebben we gevraagd om vragenlijsten in te vullen over onder andere, de bij hen gestelde diagnose, de mate van astmacontrole (ACQ), het aantal astma aanvallen, het rookgedrag en de zorgconsumptie.

Van de ruim 750 onderzochte patiënten met astma had 60% een ongecontroleerd astma volgens de score van de astmacontrole vragenlijst. Bij de 540 onderzochte patiënten met een mengbeeld van astma en COPD bedroeg dit 73%. Op grond van het aantal keren dat de apotheek aan de patiënten hun medicatie verstrekte, konden we berekenen hoeveel inhalaties van de ontstekingsremmers de patiënten gemiddeld per dag gebruikten. Uit dit onderzoek bleek dat driekwart van de patiënten niet consequent de voorgeschreven hoeveelheden inhalatiemedicatie ophaalde, onafhankelijk van of zij een goede of slechte astmacontrole hadden. Hieruit valt te concluderen dat het minder goed gebruiken van de onderhoudsmedicatie niet als belangrijkste oorzaak van ongecontroleerd astma gezien kan worden. Tegen onze verwachting in haalden de patiënten met een slechte astmacontrole vaker en meer medicatie op dan voorgeschreven en patiënten met een goed astmacontrole veelal minder vaak. Dit suggereert dat patiënten niet zozeer de noodzaak voelen om hun inhalatie medicatie te continueren als hun astma onder controle is en meer medicatie gaan gebruiken wanneer hun astma niet onder controle is. Onvoldoende ophalen van medicatie komt veel voor en lijkt niet gerelateerd aan slechte astma controle. Het is daarom waarschijnlijk dat er andere factoren zijn die bijdragen aan verlies van astmacontrole dan het onvoldoende gebruiken van medicatie.

Astma zelfmanagement en patiënt gerelateerde factoren

Een goede astmacontrole vraagt om zorgvuldig zelfmanagement. Effectief zelfmanagement omvat therapietrouw, adequate inhalatietechnieken en zelfmonitoren. Zelfmonitoren betekent het herkennen van symptomen met als doel de medicatie en de dagelijkse activiteiten aan te passen. Dit vereist dat de patiënt kennis heeft over de ziekte en de prikkels die een negatieve invloed kunnen hebben op astmacontrole. Zelfmanagement vraagt veel van de patiënt. Gezien de hoge eisen die zelfmanagement taken stellen aan de vaardigheden van de patiënt is het duidelijk dat persoonlijke factoren een rol spelen in het al dan niet slagen in goed zelfmanagement. Daarmee bepalen persoonlijke factoren naast de genetische ernst van de ziekte de gezondheidstoestand van de patiënt. Tegelijkertijd heeft astma complexe gevolgen, niet alleen op lichamelijk, maar ook op emotioneel, cognitief, gedragsmatig en sociaal gebied. Daardoor is astma veelzijdig en kent verschillende

verschijningsvormen (fenotypen). Naar deze zogenaamde fenotypen van astma wordt veel onderzoek gedaan, omdat het aannemelijk is dat deze fenotypen om verschillende behandelingen vragen.

Fenotype studies laten inderdaad zien dat symptomen en de klinische presentatie van het astma niet alleen door de ernst van de onderliggende ziekte worden verklaard. De onderlinge dynamiek tussen de ziekte astma, persoonlijke factoren en gevolgen op alle gebieden bepalen hoe de symptomen en de klinisch presentatie zijn. Deze kan zeer verschillend zijn. Het beslaat een wijd spectrum van enerzijds patiënten die ernstige luchtwegvernauwing en ontsteking hebben, maar weinig klachten ervaren, anderzijds zijn er patiënten die lijden aan heftige benauwdheid, zonder dat er objectief een luchtwegvernauwing kan worden vastgesteld. Daarnaast zijn ook alle variaties en combinaties van deze overwegend ontsteking gerelateerde en symptoom gerelateerde fenotypen mogelijk.

Bij moeilijk te controleren astma is het van belang om ziekte en patient gerelateerde gebieden van de gezondheidstoestand te onderzoeken en een duidelijk beeld te krijgen van het complex van factoren dat een rol speelt. Hoe kunnen we daar zicht op krijgen?

De meest gebruikte vragenlijsten bij astma zijn de Astma Controle Questionnaire (ACQ) en de Astma Kwaliteit van Leven vragenlijst (AQLQ). De ACQ is gericht op vragen over symptomen, beperkingen in activiteiten, noodmedicatie gebruik en de longfunctie. De AQLQ stelt daarnaast vragen met betrekking tot het emotioneel functioneren van de patiënt en de invloed van omgevingsfactoren op astmacontrole. Deze vragenlijsten geven geen compleet beeld van de verschillende gebieden van de gezondheidstoestand van de patient.

Een integraal instrument voor de gezondheidstoestand was nog niet voor handen voor astma, maar wel voor COPD, namelijk het Nijmegen Clinical Screening Instrument (NCSI). We hebben onderzocht of het NCSI, dat informatie verzamelt op ziekte en patiënt gerelateerde gebieden voor COPD, ook voor patiënten met moeilijk te controleren astma gebruikt kan worden *(hoofdstuk 3)*. Hiertoe hebben we bij patiënten die in het Merem Nederlands Astmacentrum Davos waren opgenomen, een vergelijkend onderzoek gedaan. In onze studie *(hoofdstuk 3)* hebben we kunnen aantonen dat de NCSI bij moeilijk te controleren astma gebruikt kan worden en een goed instrument is om de klinische, fysiologische, functionele en psychosociale gebieden in kaart te brengen. Het is dus aannemelijk dat het NCSI ook bij astma een vollediger beeld geeft omdat ziekte specifieke kenmerken samen met patiënt gerelateerde factoren (de scores op de vragenlijsten) in beeld worden gebracht.

Het onderzoeken van alle onderliggende factoren van de klinische presentatie is een enorme uitdaging, zeker bij moeilijk te controleren astma. Onze studie toont aan dat de NCSI bruikbaar kan zijn in dit proces. Daarbij kunnen met behulp van de daaruit afgeleide PatiëntProfielKaart probleemgebieden snel geïdentificeerd worden, hetgeen de NCSI een praktisch instrument maakt voor de dagelijkse zorg. In een optimale vorm zou het NCSI aangevuld moeten worden met ontstekingsmarkers en met vragen over therapietrouw.

Omgeving gerelateerde factoren

Allergenen en astmacontrole

Talloze omgevingsfactoren, allergische en niet-allergische, kunnen astma luxeren en daardoor invloed uitoefenen op de controle van astma. De huisstofmijt wordt sinds decennia wereldwijd als een belangrijke allergeenproducent gezien. Bij patiënten met een huisstofmijt-allergisch astma leidt blootstelling aan huisstofmijt-allergenen veelal tot astma symptomen en verlies van astmacontrole. Het is dan ook alleszins redelijk dat internationale richtlijnen allergeenvermijding adviseren. Het effect van allergeen vermijding, ofwel saneringsmaatregelen, is echter niet onomstotelijk bewezen. Omdat het bed beschouwd wordt als een belangrijke plek waar huisstofmijten voorkomen wordt het verminderen van blootstelling aan huisstofmijt allergenen in bed vaak als een eerste doel gezien. Dat kan met speciale huisstofmijt on-doorgankelijke matrashoezen.

Om het effect van deze speciale hoezen te kunnen bepalen hebben we het lange termijn effect van deze hoezen na een jaar gebruik vergeleken met zogenaamde “nephoezen” bij 30 patiënten met matig tot ernstig astma en een huisstofmijt allergie in Nederland *(hoofdstuk 4)*. Uit ons onderzoek bleek dat de werkzame hoezen de concentratie huisstofmijtallergeen significant verminderden ten opzichte van de “nephoezen”. Er werd echter geen verschil tussen beide groepen gezien in astmacontrole en kwaliteit van leven. Onze studie toonde aan dat deze matrashoezen alléén niet effectief zijn om de astmacontrole te verbeteren. De resultaten van onze studie bevestigen de resultaten van andere studies bij patiënten met astma, die ook gevonden werden bij patiënten met allergische neusklachten en eczeem.

Betekent dit dat saneringsmaatregelen nutteloos zijn?

De negatieve resultaten van studies waarin één saneringsmaatregel werd bestudeerd hebben er toe geleid dat saneren geleidelijk aan uit het behandelarsenaal verdween en artsen de interesse in omgevingsfactoren verloren. De vraag is of dit terecht is.

Om meer informatie te verzamelen over de uitwerking van allergeenvermijding op de luchtweggevoeligheid en het allergische proces hebben we verder onderzoek gedaan naar de allergische reactie *(hoofdstuk 5)*. We hebben voorafgaand aan en een jaar na het gebruik van de matrashoezen, bij de patiënten luchtweg- en huidprovocaties gedaan met huisstofmijt-allergeen extracten. Vervolgens hebben we in het bloed gekeken naar de aantallen, bij de allergische reactie betrokken, witte bloedcellen (eosinofielen). Bij de groep patiënten die nephoezen hadden gekregen vonden we een versterkte vroege reactie van de luchtwegen na de blootstelling aan huisstofmijten en een verhoogd aantal eosinofielen in het bloed. Bij de groep patiënten met de werkzame hoezen werden op deze punten geen significante veranderingen gemeten. Dit suggereert, dat de hoezen wel beschermen tegen een versterking van de allergische reactie, zoals dat gezien wordt bij blijvende blootstelling. Ook in een andere studie wordt tijdens experimenteel herhaalde blootstelling aan lage doseringen huisstofmijtallergeen dit verschijnsel van versterking van de ontsteking gemeten, zonder dat de patiënten op dat moment klachten hadden. Dit zijn studieresultaten die het verhoogde risico op toekomstig controleverlies bij voortdurende blootstelling aan allergenen bevestigen.

Talloze studies tonen de belangrijke rol van blootstelling aan allergische en niet- allergische prikkels bij astma aan. Samengevat: In grote epidemiologische studies is het hebben van antistoffen tegen huisstofmijt en schimmels nauw verbonden met de ernst van astma.

Allergische patiënten die worden blootgesteld aan een of meer allergenen hebben een verhoogde vatbaarheid voor door virussen veroorzaakte astma-aanvallen en lopen een groter risico opgenomen te worden in het ziekenhuis. Ook indirecte blootstelling aan allergenen, zoals bijvoorbeeld aan huisdier allergenen van andere kinderen in klaslokalen kan de oorzaak zijn van het verslechteren van astmacontrole. Studies hebben aangetoond, dat maatregelen die zoveel mogelijk factoren aanpakken, beter werken dan wanneer slechts de expositie aan één specifieke allergeen, zoals bij het gebruik van matrashoezen, wordt verminderd. Op grond van deze bevindingen is het aannemelijk dat allergeenvermijding gezien moet worden als een belangrijke interventie bij moeilijk te controleren astma. Gelukkig besteden in Nederland met name longverpleegkundigen in de dagelijkse praktijk hier veel aandacht aan. Een voorwaarde voor effectieve sanering is op zijn minst een betekenisvolle vermindering van de voor de patiënt relevante allergenen *(hoofdstuk 5)*.

Niet allergische prikkels en astmacontrole

Luchtverontreiniging

Van de niet-allergische prikkels die bijdragen aan een slechte astmacontrole is de luchtverontreiniging de belangrijkste. Voor het desastreuze effect van luchtverontreiniging

op de luchtwegen komt steeds meer bewijs. Luchtverontreiniging leidt tot toename van luchtwegontsteking en luchtweggevoeligheid en daarmee tot verstoring van de astmacontrole. Luchtverontreiniging kan ook het effect van de allergische reactie en virusinfecties intensiveren en daarmee ondermeer leiden tot ziekenhuis opnames. Volwassenen, maar ook en vooral kinderen, die dichtbij snelwegen wonen hebben een verhoogd risico op negatieve effecten door de voortdurende blootstelling aan luchtverontreiniging.

Externe stress factoren

Tabaksrook, scherpe geuren, schoonmaakmiddelen, beroepsmatige stoffen en aan weersomstandigheden gerelateerde factoren, zoals mist en regen zijn eveneens bekende prikkels die astmacontrole kunnen verstoren. Daarnaast komen steeds meer studies die de invloed van acute en chronische stress, zoals "life events" en traumata op het verlies van astmacontrole beschrijven.

Patiënt- en omgeving gerelateerde factoren gekoppeld.

Hooggebergte behandeling en astmacontrole

De eerste waarneming van het gunstige effect van het hooggebergte klimaat op astma werd al in 1879 gedaan, in een tijd dat patiënten met tuberculose in Davos herstel zochten. Sindsdien zijn ook patiënten met astma naar Davos verwezen en zijn er veel studies gedaan, die het heilzame effect op astmacontrole, op de gevoeligheid van de luchtwegen, op ontstekings- kenmerken en op het gebruik van prednisolon hebben aangetoond bij kinderen en volwassenen met een allergisch astma *(hoofdstuk 7)*.

De hooggebergte omgeving (1600 m boven zeeniveau) wordt gekenmerkt door een lage relatieve luchtvochtigheid met sterk verminderde concentraties huisstofmijt, pollen en schimmelsporen. Ver van de geïndustrialiseerde stadsomgeving wordt in Davos veel minder luchtverontreiniging gemeten. Dit bergklimaat biedt bovendien hoge blootstelling aan UV licht met mogelijke afweer verhogende werking. De afstand tot Nederland biedt mogelijke vrijheid van psychosociale stress *(hoofdstuk 7)*.

Het onderzoek naar het effect van hooggebergtebehandeling bij allergische patiënten hebben wij aangevuld met onderzoek bij niet-allergische patiënten *(hoofdstuk 8)*. Het effect van hooggebergte behandeling gedurende 12 weken bij niet allergische patiënten werd vergeleken met het effect bij allergische patiënten. Beide groepen lieten een overeenkomstige significante verbetering zien in astmacontrole en kwaliteit van leven, afname van bovenste luchtwegklachten, en een verbeterde longfunctie en inspanningstolerantie. Bijna de helft van de patiënten met een huisstofmijtallergie en een derde van de niet-allergi-

sche patiënten konden de onderhoudsdosering prednisolon volledig stoppen, terwijl bij de overige patiënten de dosis aanzienlijk verlaagd kon worden. Op basis van deze uitkomsten hebben we geconcludeerd dat hooggebergte-behandeling de astmacontrole bij zowel allergische als bij niet-allergische patiënten verbetert en de mogelijkheden vergroot om thuis weer een zo normaal mogelijk leven te leiden

Wat is de verklaring voor het heilzame effect van hooggebergte-behandeling?

Luchtwegovergevoeligheid, de zogenaamde hyperreactiviteit voor prikkels, is een karakteristiek kenmerk van astma en niet alleen van allergisch astma. Een prikkelvrije omgeving zoals in Davos is derhalve effectief voor allergische en niet-allergische patienten. Minder prikkels betekent minder irritatie en ontsteking, minder symptomen van benauwdheid en hoest, meer mogelijkheden om te bewegen en te sporten. De objectieve verbetering in inspanningsvermogen na hooggebergte-behandeling is hiervoor een sterke aanwijzing.

Over het algemeen wordt aangenomen dat met name de lage blootstelling aan prikkels in het bergklimaat de chronische ontsteking tot rust brengt, waardoor het astma onder controle kan komen. Dit mechanisme kan gezien worden als identiek aan maar een omkering van het proces zoals we dat beschreven in *hoofdstuk 5*. Bij voortdurende blootstelling aan allergenen tijdens het gebruik van "nephoezen" gedurende een jaar is daar sprake van toenemende allergeen gevoeligheid en ontsteking.

Bovendien veronderstelt men dat blootstelling aan twee of meerdere luchtwegontsteking stimulerende prikkels centraal staat bij het ontstaan van meer ernstige luchtwegziekten. Volgens deze " multipele hit hypothese" zou door vermijding van deze prikkels de progressie van de onderliggende ziekte kunnen verminderen en astma controle kunnen herstellen.

Dergelijke mechanismen helpen ons te begrijpen waarom de prikkelarme omgeving van Davos bij zowel allergische als niet-allergische patiënten het luchtweg slijmvlies beschadigende proces kan verminderen, waardoor de astmacontrole kan worden hersteld.

Hooggebergte-behandeling combineert de prikkelarme omgeving met behandeling op maat. De intensieve multimodale behandeling door een interdisciplinair team van experts op medisch, verpleegkundig, fysiotherapeutisch, beweegkundig en psychologisch gebied, is gebaseerd op het astma fenotype en de integrale gezondheidstoestand van de patiënt.

Bij de groep patiënten met ongecontroleerd astma, ondanks maximale behandeling in Nederland, werd een aanzienlijke verbetering in astma controle bereikt.

Nieuwe geneesmiddelen, zoals monoclonale antistoffen tegen IgE (omalizumab) en Interleukine-5 (mepolizumab) blijken in vergelijking tot deze hooggebergte resultaten, tot slechts relatief kleine verbeteringen in kwaliteit van leven te leiden. Ook andere niet-farmacologische behandelingen, zoals thermoplastiek laten in deze heterogene groep patiënten met ernstig, moeilijk te controleren astma eveneens beperkte verbeteringen zien.

De kracht en beperkingen van dit proefschrift

Dit is de eerste studie die zowel patiënt gerelateerde als omgevingsfactoren onderzoekt in relatie tot astma controle. We konden niet alle beïnvloedende factoren onderzoeken, maar wel de meest belangrijke. We bestudeerden patiënten uit de eerste, tweede en derde lijn en onderzochten enerzijds het effect van een eenvoudige sanerings maatregel en anderzijds van een intensieve behandelprogramma in het hooggebergte. We concludeerden dat matrashoezen als enige saneringsmaatregel niet klinisch effectief zijn, terwijl de uitgebreide prikkel vermijding in Davos in combinatie met multimodale behandeling op maat van het persoonlijk profiel significant effect heeft in een groep patiënten met moeilijk onder controle te krijgen astma.

Naast de beperkte keuze van het aantal onderzochte factoren in de studies van dit proefschrift, zijn er ten aanzien van de studie naar de effecten van hooggebergte-behandeling nog de volgende beperkingen te noemen.

Op de eerste plaats hadden we, vanwege beperkte middelen, niet de gelegenheid om hoog gebergte behandeling te vergelijken met een zelfde behandeling op zeeniveau. Een dergelijke vergelijkende studie over de specifieke bijdrage van het prikkelarme bergklimaat is recent gestart.

Op de tweede plaats verdient onze aanname dat multimodale behandeling essentieel is om astmacontrole te bereiken in deze groep patiënten met moeilijk te controleren astma nader onderzoek. Een studieopzet die het mogelijk maakt patiënten die hooggebergte behandeling ontvangen te vergelijken met patiënten die alleen in het hooggebergte verblijven, zonder specifieke behandeling, zou ons hierover meer informatie kunnen geven. Ook moet nog nader worden onderzocht wat de lange termijn effecten van hooggebergte-behandeling op astmacontrole zijn.

Tenslotte, om het klinische tot rust komen van de ontsteking te onderbouwen, zouden we nader onderzoek moeten doen naar de luchtweg ontsteking met behulp van opgewekt sputum of luchtweg biopten. De mogelijkheden daartoe ontbreken in Davos, omdat een dergelijk onderzoek vraagt om een gespecialiseerd laboratorium.

Wat kunnen de resultaten van het hier gepresenteerde onderzoek betekenen voor de praktijk?

Medicatiegebruik en gezondheidstoestand van de patiënt

Om goede controle over astma te bereiken zijn een aantal punten van belang:

Uit onze studie blijkt dat veel patiënten hun medicatie niet consequent bij de apotheek ophalen en waarschijnlijk niet volgens voorschrift gebruiken, zowel de patiënten die hun astma onder controle hebben als zij die een slechte astmacontrole hebben. Het bespreken van het gebruik van medicatie zou daarom tijdens gesprekken tussen arts en patiënt regelmatig aan de orde gesteld moeten worden, ook al is dit een lastig onderwerp. Het is raadzaam om de patiënt op een niet-oordelende manier te vragen hoe vaak medicatie- inname gemist wordt en of de patiënt last heeft van bijwerkingen van de medicatie. Een goede therapeutische relatie is een absolute voorwaarde voor een goede samenwerking tussen de patiënt en de voorschrijver. Alleen dan kan overeenstemming worden bereikt over het gebruik van medicatie. (coherence in plaats van compliance).

Een goed behandeladvies zou gebaseerd moeten zijn op de afweging van de klinische, fysiologische, inflammatoire, functionele en psychosociale gebieden van de gezondheidstoestand van de patient. De NCSI kan daarbij een zinvol instrument vormen.

Prikkelvermijding is belangrijk

Matrashoezen verminderen de blootstelling aan huisstofmijt allergenen gedurende de nacht, maar hebben niet direct invloed op astmacontrole. Matrashoezen als enige saneringsmaatregel helpen onvoldoende. Saneringsmaatregelen moeten zoveel mogelijk alle voor de patiënt relevante allergische en niet–allergische prikkels betreffen, gedurende de dag en nacht. Met name wanneer ongecontroleerd astma samengaat met aanwijzingen van verhoogde ontsteking in de luchtwegen, is het van belang om omgevingsfactoren op te sporen die het astmatische proces prikkelen en onderhouden. Het zo goed mogelijk saneren van deze factoren blijft een belangrijke stap in astma management zowel bij patiënten met een allergisch als bij patienten met een niet-allergisch astma. Naast de blootstelling aan allergische en niet-allergische prikkels spelen ook de individuele gevoeligheid voor prikkels, de persoonlijke mogelijkheden om prikkels te vermijden en de perceptie van de ziekte een rol. Een op de individuele patiënt afgestemd behandeladvies, gebaseerd op de patiënt karakteristieken en blootstelling aan prikkels, moet ook educatie en instructie bevatten over methodes om risicofactoren te vermijden.

Patiënt gerelateerde en omgevingsfactoren gecombineerd

Voor patiënten met ernstig en moeilijk onder controle te krijgen astma, is een combinatie van

een prikkelarme omgeving en de multi-modale expert behandeling gebaseerd op het astma fenotype en de integrale gezondheidstoestand van de patient optimaal. Deze mogelijkheid wordt geboden in het Merem Nederlands Astmacentrum Davos (NAD). Deze combinatie biedt een relevante en klinisch effectieve interventie. Patiënten die ondanks maximale behandeling in Nederland de zware last dragen van een blijvend slechte astmacontrole, moeten de gelegenheid krijgen om gebruik te kunnen maken van deze effectieve behandeling.

Slot opmerkingen

In dit proefschrift is de focus gericht op niet-medicamenteuze factoren die van invloed zijn op astmacontrole. Patiënt gerelateerde factoren en omgeving gerelateerde factoren zoals blootstelling aan allergenen en luchtverontreiniging, spelen een rol in de verstoring van astmacontrole. Wanneer astma niet onder controle is, is de zoektocht naar de invloed van deze factoren een belangrijke stap. Doelgerichte interventie, gebaseerd op deze specifieke factoren biedt kansen om astmacontrole te bereiken bij patiënten met ernstig en moeilijk te controleren astma.

Op basis van de voor dit proefschrift gedane studies trekken wij de volgende conclusies in relatie tot astmacontrole:

1. Zorgvuldig medicatie gebruik is een belangrijke onderwerp zowel bij patiënten met een goede en slechte astmacontrole en zou bij elk patiëntcontact aan de orde gesteld moeten worden.

2. Het meten van klinische, fysiologische, inflammatoire, functionele en psychologische domeinen met behulp van de NCSI geeft een veelomvattend beeld van de karakteristieken van de patiënt met ongecontroleerd astma en identificeert factoren en patronen die astmacontrole kunnen beïnvloeden.

3. Saneren van risicovolle omgevingsfactoren blijft een belangrijk onderdeel van astma behandeling. Op maat geleverde patiëntadviezen moeten gericht zijn op allergische en niet-allergische prikkels. Daarnaast moeten deze adviezen educatie bevatten over behoud van astma controle.

4. Hooggebergte behandeling biedt patienten met ernstig en moeilijk te controleren astma een effectieve mogelijkheid om astma controle te verwerven. De combinatie van de prikkelarme omgeving en de multi-modale expert behandeling gebaseerd op het astma fenotype en de integrale gezondheidstoestand van de patient zijn daarbij de pijlers van de behandeling.

Dankwoord en Curriculum Vitae

Dankwoord

Vele mensen hebben bijgedragen aan dit proefschrift en wil ik hier van harte danken. Op de eerste plaats wil ik mijn dank uitspreken aan alle patiënten die bereid waren mee te werken aan de verschillende studies. Hun enthousiasme en overtuiging waren en zijn voor mij een grote bron van inspiratie.

Mijn wetenschappelijke arbeid begon in het astmacentrum Heideheuvel te Hilversum. Eind negentiger jaren kreeg ik van Siety de Jager de kans om het wetenschappelijk onderzoek te gaan organiseren. Dankzij Jan de Monchy zette ik in samenwerking met Marjolein Weller, zelf de eerste stappen op het pad van wetenschappelijk onderzoek. Saneringsmaatregelen en met name matrashoezen waren in opmars. Ook het Nederlands Astma Fonds vond het van belang dat het effect van allergeen ondoorgankelijke hoezen zorgvuldig onderzocht werd en sponsorde onze dubbelblind gerandomiseerde studie. We zijn hen daarvoor zeer dankbaar. Met name bij de beschrijving van de resultaten en de totstandkoming van de publicaties werden we in het bijzonder door Dirkje Postma gesteund en geïnspireerd. Mijn toenmalige collegae longartsen en huidige collegae in Heideheuvel, Ineke Kok en Ton van Keimpema, Ramela Asfazadour, David de Vries en Eline bij de Vaate dank ik voor hun steun. Van alle bij het onderzoek betrokken medewerkers wil ik vooral Corine Coppens, Alice Scholtens en Christien Tamminga bedanken. En Ineke Bregman, zij heeft voor het onderzoek talrijke matrassen van huisstofmijten ontdaan en daarmee een grote slachting aangericht onder de populatie van dit schadelijke wezentje.

In 2001 werd ik gevraagd om te komen werken in het Nederlands Astmacentrum Davos (NAD). Ik werd al snel enthousiast over de gunstige effecten van hooggebergte behandeling. Vrijwel alle patiënten bereikten in het NAD goede tot zeer goede behandelresultaten, die ik nooit eerder zo gezien had. Dat inspireerde mij om de wetenschappelijk onderzoekstraditie van het NAD voort te zetten. Daar was een stevige netwerk en inbedding in de Nederlandse gezondheidzorg voor nodig. Het was mij een genoegen om met longartsen met speciale belangstelling voor ernstig en moeilijk te behandelen astma het Nederlands Ernstig Astma Research (NEAR) netwerk op te zetten. Deze groep inventariseerde in eerste instantie de diagnostiek en behandelmogelijkheden. Daarna werd er gewerkt aan de Richtlijn Ernstig Astma. Els Weersink, Liesbeth Bel, Anneke Ten Brinke, Bert Roldaan, Gert-Jan Braunstahl ben ik dankbaar voor hun inspiratie en samenwerking. Met name dank ik Bert als gepassioneerde collega met uitgebreide ervaring op het gebied van hooggebergtebehandeling. Ook de goede samenwerking met de NVALT en haar leden, mijn collega longartsen, alle voorzitters met in het bijzonder Geert-Jan Wesseling en Yvonne Heijdra en het secretariaat is voor mij en het NAD nog steeds een voorrecht.

Onderzoek doen in een klein, primair op zorg gericht centrum ligt niet voor de hand.

Frank Weller wil ik bedanken dat hij mij in 2007 in staat stelde om met mijn hooggebergte studie te starten en de huidige Raad van Bestuur, Gerard Hoogvliet, om het voort te zetten en af te ronden. Met financiële ondersteuning van de Vereniging Nederland Davos (VND) werd het mogelijk om een uitgebreide observationele studie op te zetten. Liesbeth Bel ben ik zeer erkentelijk voor de eerste onderzoekschets die zij destijds maakte.

Iedereen in het NAD bleek steeds bereid om mij te helpen het onderzoek in goede banen te leiden, van het informeren en inplannen van patiënten voor de reguliere metingen tot het soepel laten verlopen van de testen. Roderick Jansen, Jeanette Ambuhl, Harriet Grachten, Miriam Ambuhl, Elvira Sinnighe, Maaike Zantema, Lucie Roeken, Marja Hartman, Irene Ciocci, Anja Verstegen, Mathi Duijs, Charlotte Lemmens, Aad Verschie, en alle anderen die voor kortere of langere tijd in het NAD werkten, bedank ik voor hun niet aflatende assistentie. Aad Bron heeft in die tijd een groter deel van de patientenzorg op zich genomen. Zijn aanvankelijke terughoudendheid maakte al gauw plaats voor zinnige kritiek en waardevol advies. Ook mijn collegae kinderartsen, Henk Verweij, Ad Bosschaert, Jan Bart Yntema en Maartje Vandewall, en collegae psychologen onder andere Geert Mensing, Renate Nicolaas, Joan Winkelhof en Janneke Delsing waren altijd steunend en bemoedigend.

In deze jaren heeft Karin Fieten mij geholpen met de dataverzameling en -analyse. Ik ben er trots op dat zij binnenkort haar eigen promotieonderzoek bij kinderen met eczeem en astma afrondt.

Wetenschappelijk onderzoek ver weg van Nederland, boven op een berg is vrijwel niet mogelijk zonder de bijvoeding in een academisch ziekenhuis. De afdeling van Liesbeth Bel heeft mij van het begin af aan verwelkomd als een van hun gelijken. Simone Hashimoto, Marijke Amelink, Nikki Fens, Selma de Nijs, David Yick, Paul Brinkman, Guus Westerhof en Pieter Paul Hekking wil ik van harte bedanken voor hun collegiale ondersteuning en motiverende gesprekken. Met name Simone bleek een uitstekende coach, die mij vele malen redde en een hart onder de riem wist te steken. Jacquelien van de Vlies hielp mij op kritieke momenten. Op de achtergrond stonden zo nodig Peter Sterk en Koos Zwinderman altijd voor mij klaar.

Els Weersink , mijn copromotor, was voor mij een rotsvast steunpunt. Haar wil ik speciaal bedanken voor haar relativerende opmerkingen, pragmatische oplossingen en vertrouwen in de goede afloop van het promotietraject. Vervolgens, maar niet in het minst wil ik Liesbeth bedanken. Als je promovenda in Zwitserland vertoeft, is effectieve begeleiding niet altijd gemakkelijk. Dat klemt temeer waar het NAD niet te vergelijken valt met een acade-

misch ziekenhuis. Ook het feit dat ik aan het einde van mijn carrière promoveer, in plaats van het begin, draagt eraan bij dat er aan begeleiding andere eisen worden gesteld. Ik ben Liesbeth erkentelijk dat ze ondanks dit alles met mij dit project heeft aangedurfd en mij steeds kritisch ter zijde heeft gestaan.

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Een goede vriendenkring is goud waard, niet alleen bij dit promotie project. Dank aan mijn lieve paranimfen Olga van den Berg en Annemiek Mellink, mijn vriendinnen Marceline Ingenhoes-Kortenbout en Shelley Overbeek voor alles wat jullie hebben gedaan. Ook wil ik hier Ton Hagenbeek, Piet en Carla Bruijnzeel, Suzanne Pasmans, Jon Vismans, Willemijn Vismans en Margreet van Roest bedanken voor hun adviezen.

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Ik ben dankbaar dat ik heb bij mogen dragen aan de wetenschappelijke onderbouwing van hooggebergte behandeling en dat het onderzoek wordt voorgezet. Binnenkort komen de resultaten van de “Davos trial”, de pragmatische gerandomiseerde gecontroleerde studie van hooggebergte behandeling en de actuele best care van Nederlandse kinderen met ernstige atopische dermatitis (en astma) onder leiding van Susanne Pasmans.

In samenwerking met Jaap Sont hebben we de “Practiss” studie uitgevoerd, waarbij internet based zelfmanagement ondersteuning in de nazorg vergeleken wordt met usual care bij patiënten die in Davos behandeld en weer terug in Nederland zijn.

Tenslotte ben ik zeer verheugd dat het hooggebergte onderzoek voortgezet wordt met een bijzondere gerandomiseerde gecontroleerde pragmatische studie onder leiding van Jan Willem Lammers en Anita Beelen, waarbij de effecten van Hooggebergte behandeling bij patiënten met ernstig refractair astma vergeleken gaan worden met klinische longrevalidatie op zee niveau in het MEREM behandelcentrum Heideheuvel.

Ik vertrouw erop dat we daarmee het overtuigend argument voor hooggebergte-behandeling krijgen voor de zorgverzekeraars en het Zorginstituut Nederland die daarom hebben gevraagd.

Hooggebergtebehandeling is en blijft een unieke mogelijkheid voor patiënten met moeilijk te controleren astma, die ondanks hoog medicatie gebruik veel klachten blijven houden. Het Nederlands Astmacentrum Davos vormt voor deze relatief kleine groep vaak nog de enige kans op verbetering. .

Curriculum Vitae

Lucia Rijssenbeek-Nouwens werd geboren in Oegstgeest en volgde het Gymnasium aan het Agneslyceum in Leiden. Na in Leiden aan de studie geschiedenis geproefd te hebben, kreeg zij in 1974 de kans om, als een van de eerste lichting studenten aan de Universiteit van Maastricht, geneeskunde te studeren. Zij behaalde in 1980 haar artsexamen. Van 1980 - 1985 volgde zij haar opleiding tot longarts onder leiding van Professor dr. L. Greve in het ziekenhuis St Annadal, later Academisch Ziekenhuis te Maastricht.

In 1985 ging zij werken in het Astmacentrum Heideheuvel en daarnaast in het Oude Rijn ziekenhuis samen met longarts Janke van den Beukel. In 1989 concentreerde zij haar werkzaamheden in Heideheuvel en nam naast haar klinisch werk de taak van Hoofd medische dienst voor 4 jaar op zich. Vanaf 1994 werd zij coördinator wetenschappelijk onderzoek. In eerste instantie werd het focus gelegd op het onderzoek van allergeen werende matrashoezen onder leiding van Professor dr. Jan De Monchy en later Professor dr. Dirkje Postma.

Vanaf 2001 werkt zij in het Nederlands Astmacentrum Davos (NAD), waar ze vanaf 2006 haar wetenschappelijk werk onder leiding van Professor dr. Elisabeth Bel heeft voortgezet.

Publicaties:

1. Comparing high altitude treatment with current best care in Dutch children with moderate to severe atopic dermatitis (and asthma): study protocol for a pragmatic randomized controlled trial (DAVOS trial).
Fieten KB, Zijlstra WT, van Os-Medendorp H, Meijer Y, Venema MU, Rijssenbeek-Nouwens L, l'Hoir MP, Bruijnzeel-Koomen CA, Pasmans SG.
Trials 2014 Mar 26;15:94.

2. Health status measurement in patients with severe asthma.
Peters JB, Rijssenbeek-Nouwens LH, Bron AO, Fieten KB, Weersink EJ, Bel EH, Vercoulen JH.
Respir Med 2014;108:278-86.

3. Risk of deep vein thrombosis and pulmonary embolism in asthma.
Majoor CJ, Kamphuisen PW, Zwinderman AH, Ten Brinke A, Amelink M, Rijssenbeek-Nouwens L, Sterk PJ, Büller HR, Bel EH.
Eur Respir J 2013; 42:655-61.

4. High-altitude treatment in atopic and nonatopic patients with severe asthma.
Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Bel EH, Weersink EJ.
Eur Respir J 2012; 40:1374-80.

5. High-altitude treatment: a therapeutic option for patients with severe, refractory asthma?
Rijssenbeek-Nouwens LH, Bel EH.
Clin Exp Allergy 2011; 41:775-82.

6. Patients With Aspergillus Fumigatus-Associated Asthma Show Clinical Improvement At High Altitude.
Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Bel EH.
Am J Respir Crit Care Med 2011; 183, A1277.

7. Clinical improvement in patients with severe asthma at high altitude occurs irrespective of allergy to house dust mite.
Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Weersink EJ, Sterk PJ, Bel EH.
Am J Respir Crit Care Med 2010; 181, A5416.

8. Improvement in asthma control and decrease in FENO, whilst tapering the dose of oral corticosteroids during rehabilitation at high altitude in adults with severe asthma
Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Sterk PJ, Bel EH.
Am J Respir Crit Care Med 2009; 179, A2898.

9. How persistent is "persistent airflow limitation" in severe asthma.
Rijssenbeek-Nouwens LH, Bron AO, Naves C, Weller F, Weersink EJ, Bel EH.
Eur Respir J 2006; 28 (Suppl. 50).

10. Anti-allergic mattress covers in asthma: to do or not to do?
Rijssenbeek-Nouwens LH, Oosting AJ, Bruijnzeel-Koomen CA, de Bruin-Weller MS.
Clin Exp Allergy 2003; 33:1613-7.

11. Clinical evaluation of the effect of anti-allergic mattress covers in patients with moderate to severe asthma and house dust mite allergy: a randomised double blind placebo controlled study.
Rijssenbeek-Nouwens LH, Oosting AJ, de Bruin-Weller MS, Bregman I, de Monchy JG, Postma DS.
Thorax 2002; 57:784-90.

12. Assessing inpatient pulmonary rehabilitation using the patient‘s view of outcome.
van Stel HF, Colland VT, Heins NL, Rijssenbeek-Nouwens LH, Everaerd W.
J Cardiopulm Rehabil 2002; 22:201-10.

13. The effect of anti-allergic mattress encasings on house dust mite-induced early- and late-airway reactions in asthmatic patients. A double-blind, placebo-controlled study.Rijssenbeek-Nouwens LH, Oosting AJ, De Monchy JG, Bregman I, Postma DS, De Bruin-Weller MS.
Clin Exp Allergy 2002; 32:117-25.

14. Multivariable assessment of the 6-min walking test in patients with chronic obstructive pulmonary disease.
van Stel HF, Bogaard JM, Rijssenbeek-Nouwens LH, Colland VT.
Am J Respir Crit Care Med 2001; 163:1567-71.

15. Characteristics and diagnostic significance of spontaneous wheezing in children with asthma: results of continuous in vivo sound recording.
Rietveld S, Oud M, Rijssenbeek-Nouwens LH, Vaghi D, Dooijes EH.
J Asthma 1999; 36:351-8.

16. Cough as the ambiguous indicator of airway obstruction in asthma.
Rietveld S, Rijssenbeek-Nouwens LH, Prins PJ.
J Asthma 1999; 36:177-86.

17. Diagnostics of spontaneous cough in childhood asthma: results of continuous tracheal sound recording in the homes of children.
Rietveld S, Rijssenbeek-Nouwens LH.
Chest.1998; 113:50-4.

18. Allergen-induced changes in airway responsiveness are related to baseline airway responsiveness.
de Bruin-Weller MS, Weller FR, Rijssenbeek-Nouwens LH, Jansen HM, de Monchy JG.
Allergy.1996; 51:401-6.

19. Characteristics of wheeze during histamine-induced airways obstruction in children with asthma.
Rietveld S, Dooijes EH, Rijssenbeek-Nouwens LH, Smit F, Prins PJ, Kolk AM, Everaerd WA.
Thorax 1995; 50:143-8.

20. Lack of effect of cetirizine on early and late asthmatic response after allergen challenge.
de Bruin-Weller MS, Rijssenbeek-Nouwens LH, de Monchy JG.
J Allergy Clin Immunol 1994; 94:231-9.

ASTHMA CONTROL, Patient and Environment

The goal of asthma treatment is asthma control, defined as the absence of disease manifestations. In uncontrolled asthma the search of patient related factors, as well as environmental factors is recommended.
Each patient has a unique profile of personal and environmental factors. Interventions focussed on these specific factors offer good opportunities to obtain asthma control.
High altitude treatment combines these interventions. In patients that suffer from uncontrolled asthma despite maximum pharmacological treatment high altitude treatment shows good results. Both patients with allergic asthma and non-allergic asthma achieve better asthma control.

Lucia Rijsenbeek-Nouwens is working at the Nederlands Astmacentrum Davos (NAD), Switserland. She started her career in Astmacentrum Heideheuvel in the Netherlands. Since 2001 she specialized in severe and difficult to treat asthma.