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QUALITY OF LIFE AND MARKERS OF INFLAMMATION

A STUDY OF ASTHMA IN PRIMARY CARE

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TO INGER, JENS
AND KRISTINA

ABSTRACT

Asthma is a chronic disease that usually is diagnosed and treated in primary care. Most patients have a mild to moderate disease.

Asthma is considered to be caused by inflammation of the airways. There are several conventional ways of measuring asthma severity and control: lung function, reversibility to a bronchodilator, provocation tests to investigate airway hyperresponsiveness, and measurement of exhaled nitric oxide (NO). In recent years, it has been common to incorporate an assessment of quality of life in research and practice. The aim of this thesis has been to assess the relationship between quality of life, as assessed by the Asthma Quality of Life Questionnaire (AQLQ), and these "objective" measures of airway inflammation in patients with mild disease.

In studies I and III we investigated these relationships and found no significant correlation between quality of life, as assessed by AQLQ, and those parameters in patients not treated with corticosteroids. However, in study I we found a significant correlation between quality of life and the answer to one single question about recent symptoms, as assessed by a visual analogue scale (VAS). We also found that females, smokers, ex-smokers and non-atopic patients had lower quality of life scores as compared to males, non smokers and atopic patients.

In study III we found a significant co-variation between exhaled NO and bronchial responsiveness to methacholine and dry air. About 75% of the patients had a positive methacholine test, 50% had elevated exhaled NO values, and approximately 30% were positive on the dry air provocation test.

In study IV we wanted to find out if quality of life and markers of asthma activity are influenced by inhaled steroids in patients with mild asthma. Seventy patients with mild asthma, not treated with steroids, were treated with inhaled fluticasone (250µg bid) or placebo for three months, in a random, double blind study. Quality of life scores were high already before treatment and were not significantly altered by treatment. Fluticasone induced a decrease in methacholine responsiveness ($p=0.009$), but there was no significant difference between the groups. The bronchial response to dry air was reduced by fluticasone ($p=0.005$), but not by placebo ($p=0.02$ between groups). Exhaled NO decreased in the fluticasone group ($p=0.0002$), but not in the placebo group ($p=0.02$ between groups). There was a relationship between the small change in quality of life and the reduction of exhaled NO ($r= -0.43$; $p=0.013$). Otherwise change in quality of life did not correlate with other parameters measured. Thus improvement of asthma activity markers, following treatment with inhaled steroids, is not reflected by an improvement in quality of life for patients with mild asthma.

In study II we investigated two groups of primary care patients with mild asthma who regarded themselves symptom-free, as assessed by the visual analogue scale (VAS). At a first visit we found a lower quality of life in patients with an impaired lung function, so called poor perceivers. Three months of therapy adjustment in that group resulted in a substantial improvement in quality of life, up to the same level as with the patients having an initially normal lung function. Also lung function improved, but not up to the same level as in the other group.

In conclusion, we found that the majority of patients with asthma in primary care have high quality of life scores. We found no correlation between quality of life and parameters such as lung function, reversibility to a bronchodilator, bronchial reversibility to a direct and an indirect stimuli and exhaled NO in steroid-free patients with mild asthma. There was a fairly good correlation between quality of life and VAS. In patients with mild asthma three months of steroid inhalation altered bronchial responsiveness and exhaled NO-levels, but had no effects on quality of life. We have also shown that patients with mild asthma and impaired lung function, who regard themselves as free of symptoms, experience a clinical relevant improvement in quality of life following adjustment of therapy.

Key worlds: Mild Asthma, primary care, quality of life, airway inflammation, bronchial responsiveness, fluticasone.

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LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AHR	Airway hyperresponsiveness
AIRE	The Asthma Insights and Reality in Europe study
ATS	American Thoracic Society
AQLQ	Asthma quality of life questionnaire
AQLQ(S)	Asthma quality of life questionnaire with standardized questions
BAL	Bronchoalveolar lavage
BDP	Beclomethasone dipropionate
BHR	Bronchial hyperreactivity
bid	Bis in dié, twice a day
BUD	Budesonide
COPD	Chronic obstructive pulmonary disease
DSCG	Disodium cromoglycate
ECP	Serum eosinophil cationic protein
EDN	Eosinophil-derived neurotoxin
EVH	Eucapnic voluntary hyperventilation
FEV_1	Forced expiratory volume in 1 second.
FP	Fluticasone dipropionate
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GP	General Practitioner
HRQoL	Health Related Quality of Life
ICS	Inhaled corticosteroids
IgE	Immunoglobuline E
MID	Minimal important difference
NO	Nitric oxide
NNT	Number needed to treat
PEF	Peak expiratory flow
Ppb	Parts per billion
Prn	Pro re na´ta, when required
QoL	Quality of Life
SEM	Standard error of the mean
SF-12	Short Form 12
SF-36	Short Form 36
VAS	Visual analogue scale

CONTENTS

Introduction

Background

Asthma is a chronic disease, which usually is diagnosed and treated in primary care. The majority of patients have mild to moderate asthma [Rabe et al., 2000; Rabe et al., 2004; Ställberg et al.], but the majority of published asthma studies have focused on patients with a more severe disease, patients who normally are controlled by specialists.

In clinical practice, patients are usually monitored by registration of their symptoms, physical examination, spirometry, PEF measurements and need of medication. Those measurements are valuable, but do not reflect how the patients function in their daily lives. The development of disease-specific quality of life questionnaires has made it possible to identify which impairments are the most troublesome for patients with asthma. In many asthmatic patients, physical activity such as sports, shopping or scaling stairs induces symptoms. Other factors that may trigger symptoms are environmental stimuli, such as cigarette smoke, strong smells or weather conditions interfering with social activities.

In clinical practice, symptoms have always been evaluated through simple questions. These questions have been developed into validated and reliable questionnaires that provide insights into the patients' well-being. Such questionnaires reveal functional impairments that influence daily life. Since tools for evaluation of symptoms now are available, we decided to use quality of life as the primary source of outcome in our studies.

Currently, several well validated, disease-specific quality of life questionnaires, with strong measurement properties, are available. Some of the questionnaires are short, easily understood and often in self-administrable formats. The patients can relate to the questions and know that details that are important to them are being taken into consideration [Juniper, 1997].

Asthma is currently defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role" [GINA]. The inflammation causes an increase in airway responsiveness leading to episodes of symptoms like wheezing, breathlessness, chest tightness and coughing, due to occurrences of airflow obstruction. Lung function, reversibility to a bronchodilator, airway responsiveness and markers of airway inflammation are often measured and used in clinical practice and research. Provocation tests with methacholine and eucapnic hyperventilation are used to assess airway hyperresponsiveness, and exhaled nitric oxide is measured as "objective" tests that may reflect airway inflammation.

The general aims in our studies have been to evaluate health related quality of life and its relationship to those "objective" measurements of asthma activity in patients with mild asthma. Moreover, including intervention, we have in two studies, investigated whether adjustment of therapy influences quality of life in patients with mild asthma. We have focused on patients with mild asthma representing the majority of patients who are managed in primary care.

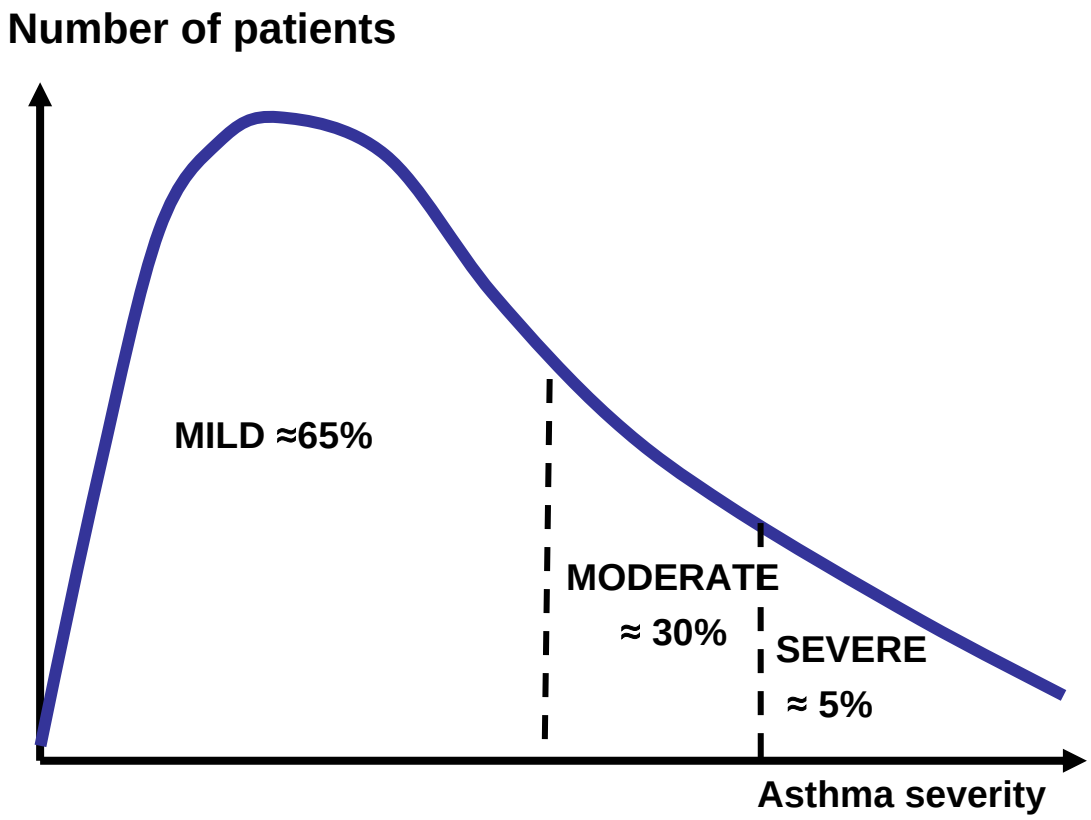

Figure 1. Asthma severity. A majority of asthma patients suffer from mild disease.

Mild Asthma

Most epidemiological data does not make distinctions among categories of asthma severity, although it is widely understood that most patients have a mild or very mild disease. In a worldwide study it was demonstrated that 59% of asthmatic patients in the U.S.A. and 63% in Western Europe suffered from mild or intermittent disease [Rabe et al., 2004]. In the European AIRE-study, 65.9% of the adult patients reported that they had no asthma symptoms during the past four weeks [Rabe et al., 2000]. In a Swedish study, 59% of the asthmatic patients in primary care only experienced symptoms "sometimes", and 26% were almost free from symptoms [Ställberg et al.]. These studies clearly indicate that a substantial number of the asthmatic patients in primary care, suffer from mild disease. In a Dutch study in primary care it was found that asthma/COPD of all severities increased, between 1977 and 1992. The increase was predominantly observed amongst those considered to have mild-to-moderate disease [Tirimanna et al.].

In the Global Initiative for Asthma, GINA, mild persistent asthma is characterised by symptoms suffered more frequently than once a week but less than once a day, nocturnal symptoms more than twice a month but less than once a week, and normal lung function between episodes without regular treatment. Intermittent asthma is characterized by symptoms less frequent than once a week, nocturnal symptoms not more than twice a month and normal lung function between episodes during treatment with low-dose inhaled steroids [GINA].

According to the GINA, asthma is considered controlled if patients have: minimal chronic symptoms; minimal or infrequent exacerbations; no emergency hospital visits; minimal use of as-needed β_2-agonists; no limitation in their activity levels; peak expiratory flow (PEF) circadian variation <20%; near normal PEF and minimal or no adverse effects from medication [GINA].
Despite the widespread acceptance of guidelines, it is obvious that many patients are not adequately treated and that the overall adherence to guidelines is poor [Taylor et al.; Legorreta et al.; Chapman et al., 2001]. There is evidence that the problems of inadequate or intermittent treatment are the most common amongst patients with mild asthma [Cockcroft et al.].

Recently, a review on the impact of "mild" asthma on health outcome has been published. A bibliographic search was run between January 1993 and August 2003. Of a total of 5.600 studies, only 39 met the inclusion/exclusion criteria: adult population, English language, stratification according to asthma severity -which should be mentioned in the abstract. The 39 studies included information on one or more of four categories: categorizing asthma severity; impact of mild asthma on health-related quality of life; impact of mild asthma on cost; impact of misclassification on management [Chapman, 2005].

It was found that asthma investigators and practitioners do not use consistent methods for asthma classification, nor any consistent definition of mild asthma. Asthma severity has been defined using a diverse range of parameters. Mild asthma has been defined according to use of medication, asthma symptoms, lung function parameters or more complex parameters and various combinations of those parameters. Asthma management guidelines were used in only three studies to assess severity [Diette et al.;Goeman et al.;Tinkelman et al.].

General practitioners tend to assess asthma severity based on patients' symptoms, rather than adhering to severity classification as advocated in the GINA guidelines. As a result, 73.4% of patients with mild intermittent asthma and 60% of patients with mild persistent asthma were under-treated due to inadequate assessment of asthma severity [Verleden et al.]. Patients themselves often underestimate the severity of their disease and are therefore at risk for under-treatment [Nguyen et al.]. Furthermore, agreement is poor about severity classification among specialists. Three pulmonary specialists who extracted clinical findings from out-patient progress notes, agreed on severity classification in only 57% of the cases [Ertle et al.].

In one study, investigating the burden of asthma satisfaction with health was strongly associated with a short-term asthma burden; 59% of the patients with mild intermittent asthma reported "very good to excellent " health, whereas only 31.6% of them with moderate to severe asthma reported a similar level of satisfaction [Fuhlbrigge et al.].

Impact of misclassification on management

There is data to support an assumption that many patients with mild asthma have not received a correct diagnosis. The consequences of being inappropriately categorized as having mild asthma could be: under-medication, inadequate symptom control, and not being treated according to asthma management guidelines.

The patients are often inadequately treated, thus not according to current guidelines. As part of the European Community Respiratory Survey, non-selected patients) with asthma (22 to 44 years of age, in two French cities, were examined to assess possible under-treatment.

According to the international guidelines, among the patients who required anti-inflammatory treatment 86.4% were under-treated in Paris and 66.7% in Montpellier. Moreover, of the patients with severe asthma, 60-85%, were not receiving anti-inflammatory treatment [Bousquet et al.]. In one study, 62% of the patients were under-treated with medication as compared to the consensus guidelines. Many patients lack a basic knowledge of their disease and its treatment [Taylor et al.]. A large number of patients with mild asthma are not taking any medication. In Italy, 76% of mild asthmatics were on inadequate doses of inhaled corticosteroids. The most frequent deviation from international guidelines was the lack of drugs for quick relief (35.8%). A large number of subjects received an annual amount of maintenance therapy covering less than 150 days over a one year period [Poluzzi et al.]. Furthermore, the use of relieve medication in relation to control medication was similar in all severity categories, indicating that the lack of disease control is as high in individuals with mild disease as in those with more severe disease. Patients reporting a higher short-term symptom burden also reported a lower level of education, lower income, and less private health insurance [Fuhlbrigge et al.]. Barr and colleagues showed that only 57% of patients with mild asthma adhered to asthma medication guidelines [Barr et al.]. One of the goals of the GINA guidelines is to achieve a normal or near normal lung function. However, in a world-wide study Rabe and colleagues found that lung function was never measured in many patients with mild asthma [Rabe et al., 2004].

Since many patients with mild asthma are under-treated, the effect of various treatment regimens has been investigated [Vermetten et al.;van Schayck et al.]. Morice and co-workers found that an initiation of treatment with anti-inflammatory therapy produced the greatest improvements in mild asthma [Morice et al.]. A consistent finding in the AIRE-study was the difference between patients´ perceived level of asthma control and reported symptom severity. There was a tendency for patients to overestimate asthma control and underestimate severity, suggesting a willingness to accept symptoms and lifestyle limitations as an unavoidable consequence of their disease [Rabe et al., 2004].

The term mild asthma may be counterproductive if it encourages under-treatment or intermittent treatment. Available data shows that classification of disease severity may be internally inconsistent and is unlikely to be applied by primary practitioners, particularly if lung function measurements are required. It is evident that most general practitioners do not follow guidelines in their clinical practise. The guidelines may not be simple enough to be used by the GP's in routine practise. It is important to develop guidelines that are acceptable for both patients and GP's and simple enough to be used in routine practice in primary care.

Quality of Life

Traditionally, the evaluation of a disease and its treatment has focused on biomedical parameters. However, the growing interest in outcomes, research has led investigators and clinicians to consider aspects that are more relevant to the patients. In recent years, the expression "Quality of Life" (QoL), frequently used in common language, has also been adopted in scientific literature. Although no formal definition of quality of life exists, it is generally recognized as a multidimensional construct that includes physical, emotional, social and practical dimensions of everyday life.

Health Related Quality of Life (HRQoL)

More specifically, Health Related Quality of Life (HRQoL) has been defined as "the impact of both illness and treatment on a patient's life as perceived by himself " [Schipper et al.]. This definition focuses on the importance of a patient's perspective, in order to obtain a realistic picture of the meaning of a disease in real life. In fact the classic outcome variables may only partly describe the burden of an illness. Assessing the subjective points of views of the patients offers a more comprehensive description of the impact of the disease and its therapy on everyday life.

Quality of life helps identify problems most frequent and troublesome for the patient, and how these problems interfere with everyday life. This aspect is of particular relevance to patients suffering from chronic diseases, where the major goals of treatment are to improve daily functioning in life and to achieve the highest possible level of well-being. Moreover, HRQoL assessment can also provide important information concerning the treatment outcome. Traditionally, HRQoL instruments are classified as generic or disease-specific.

Generic Questionnaires

Generic questionnaires have been developed to assess HRQoL in all health conditions. They allow for comparisons between patients suffering from different diseases, or between patients and healthy subjects. Generic HRQoL instruments are somewhat superficial and may be unresponsive to small but relevant changes from the patient's perspective. Therefore, the benefit of using generic instruments in clinical trials and clinical practice is limited, when treatment effects in individuals or within groups are investigated.

Short Form 36 (SF-36)

The Medical Outcomes Study Short Form 36 is a widely used generic questionnaire. The experience with SF-36 has been documented in over 1000 publications. It has been useful in comparing general and specific populations, comparing the relative burden of diseases and differentiating the health benefits of a wide range of different treatments. The transformed SF-36 scores are standardized from 0 to 100. Higher values represent a higher quality of life. It is suitable for self-administration, computerized administration or by a trained interviewer. It takes 5-10 minutes to complete [Ware et al., 1992; Ware, 2000].

Short Form 12 (SF-12)

SF-12 is a short version of SF-36. Using 12 items the SF-12 assesses the two main dimensions of quality of life: physical and mental health. The completion of the questionnaire takes about two minutes [Ware et al., 1996].

Sickness Impact Profile (SIP)

The Sickness Impact Profile, (SIP) has been extensively used in clinical research. It contains 136 items divided into 3 domains: physical (45 items); psychosocial (48 items); and independent categories (43 items) [Bergner et al.].

Disease-specific Questionnaires

Specific questionnaires are designed to focus on dimensions particularly relevant to a specific group of patients (e. g., the elderly), a particular function (e. g., pain, sexual function) or a disease. A disease-specific questionnaire does not allow comparison between different health conditions. It is usually more sensitive to changes in HRQoL resulting from treatment.

Three fundamental reasons for treating patients are:
-to prevent any immediacy of death;
-to reduce the probability of future morbidity;
-to improve the patients' well-being.

Most conventional clinical measurement of asthma control and asthma severity assesses the status of the airways and is primarily used to measure whether the first two goals above are being achieved. In a chronic condition like asthma, where a cure is normally not attainable and therapy often is needed for a long time, quality of life is an essential outcome. The HRQoL refers to the patient's assessment of his or her current level of functioning and satisfaction, compared to what he or she perceives to be ideal.

Many studies have also shown that the correlation is weak between clinical asthma status and asthma-specific quality of life. Conventional measuring of asthma, like spirometry, symptoms, airway responsiveness, sputum analysis and use of medication, provides valuable information about the status of the airways but gives little information about functional impairment (physical, emotional and social) impacting on patients' everyday lives [Juniper, 2001 a]. Therefore, to obtain a complete picture of a patient's health status, Health Related-Quality of Life must be measured parallel to conventional clinical indexes [Juniper, 2001 a].

In clinical research and in clinical trials, it has been common to use disease-specific questionnaires as end points. Several asthma-specific questionnaires have been developed. The ones most commonly used with adult patients are the Asthma Quality of Life Questionnaire (AQLQ), The Mini Asthma Quality of Life Questionnaire (MiniAQLQ), the Asthma Control Questionnaire (ACQ), and St George's Respiratory Questionnaire (SGRQ).

Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is a disease-specific, health-related quality of life instrument developed by E. Juniper *et al*. It taps both the physical as well as the emotional impact of disease. The AQLQ takes approximately 10-15 minutes to complete at the first visit and 5 minutes at follow-up. It contains 32 items in 4 domains: activity limitation (11 items); symptoms (12 items); emotions (5 items); and exposure to environmental stimuli (4 items). Five of the 11 items in the activity domain are individualized, and the patients are asked to point out 5 activities that are limited because of asthma. The patients score their experiences during the last two weeks on a 7-point scale, where 1 indicates maximal impairment and 7 no impairment at all [Juniper et al., 1992; Juniper et al., 1993]. All items are weighted equally and mean score is calculated across all items within each domain. The overall score is the mean score of all items. A clinically meaningful change, the minimal important difference, MID, is determined to be 0.5 on the 7-point scale [Juniper et al., 1994]. There is also a self-administered form AQLQ(S) with standardized questions.

Asthma Quality of Life Questionnaire with standardized questions (AQLQ[S])

In the original AQLQ, five activity questions are selected by patients themselves. However, for long-term studies and large clinical trials, generic activities may be more appropriate. Therefore, a standardized version, the AQLQ (S), has been developed. In that version, five generic activities (strenuous activities, moderate exercise, work-related activities, social activities and sleep) have replaced the five patient-specific activities in the AQLQ [Juniper et al., 1999 a].

MiniAQLQ

The Mini Asthma Quality of Life Questionnaire is a shorter version of the AQLQ, containing 15 questions. It is easier to handle in large clinical trials and long-term monitoring than the original AQLQ. The MiniAQLQ has 5 items on symptoms, 4 on activity limitations, 3 on emotional function and 3 on environmental stimuli. Its measurement properties are good but not as strong as in the original AQLQ [Juniper et al., 1999 b].

St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire has 76 items and exists in self-administered form, for administration in face-to-face or telephone interviews. It was developed to measure impact on overall health, daily life, and perceived wellbeing. It can be used for both asthma and COPD. Dimensions carried by the questionnaire are: symptoms (frequency and severity); activity (activities that cause or are limited by breathlessness); and impacts (social functioning; psychological disturbances resulting from airway disease) [Jones et al., 1991; Jones et al., 1992].

Asthma Control Questionnaire (ACQ)

The Asthma Control Questionnaire has been developed for measurement of asthma control and is not primarily a quality of life questionnaire [Juniper et al., 1999 c]. In the original questionnaire, there are seven items, five of which concern symptoms and activity limitations, one concerning the predicted FEV_1, and one the use of β_2-agonist during the preceding week. The FEV_1 item can be omitted without changing the validity or measurement properties of the instrument at group level [Juniper et al., 2001 b].

Validation of the MiniAQLQ and the ACQ in primary care

For primary care use, there is need for brief and simple questionnaires for structural patient reported outcomes. In a study in primary care the MiniAQLQ was validated, using the AQLQ(S) as "gold standard". The ACQ was validated against the symptom domain of AQLQ(S). The MiniAQLQ and the ACQ questionnaires correlated well with the AQLQ(S). The conclusion was that the instruments are sufficiently simple and robust to be suitable for research and quality of care monitoring in primary care at group level. They may, after further validation, even be useful in the management of individual patients [Ehrs et al.].

Clinical Relevance

Minimal Important Difference (MID)

In clinical trials, it is simple to determine the statistical significance of changes in quality of life, but it has not been easy to place the magnitude of these changes in a context that is meaningful for health professionals. The minimal important difference can be defined as "the smallest difference of score in the domain of interest which the patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive costs, a change in patient management" [Jaeschke et al.]. In the AQLQ, with a 7-point scale, a within – subject score change of 0.5 represents the minimal important difference of quality of life. A change in score of 1.0 may be considered a moderate change, and a change greater than 1.5 is likely to represent a large change. Changes for improvement and deterioration are the same [Juniper et al., 1994]. In the SGRQ a difference of 4 points (0-100 scale) is considered to be the minimal important difference [Schunemann et al.].

Number Needed to Treat (NNT)

The number needed to treat, NNT, is becoming increasingly used as an index for reporting the results of clinical studies. The NNT is the number of patients who have to be treated in order to gain one clinically important improvement [Walter]. It is calculated from the proportion of patients who show an improvement or deterioration on the treatment. Presentation of clinical trial results in this manner is meaningful for clinicians and is usually easier to interpret than standard deviation and confidence intervals.

Medical Outcomes Trust (MOT)

The Medical Outcomes Trust is a non-profit organization dedicated to improving health and health care by promoting the science of outcome measurement and the development, evaluation and distribution of standardized, high-quality instruments that measure health and the outcomes of medical care. The goal of the MOT is to assure the development of high-quality instruments to measure health outcome, and to achieve standardization of instruments.

Impact of mild asthma on health-related Quality of Life

Several questionnaires have been used to assess the HRQoL in patients with mild asthma. Some are asthma-specific, such as the Asthma Quality of Life Questionnaire (AQLQ) [Juniper et al., 1992; Juniper et al., 1993], The Marks Asthma Quality of Life (MAQoL) questionnaire [Marks et al., 1992; Marks et al., 1993], the St George's Respiratory Questionnaire (SGRQ), [Jones et al., 1991; Jones et al., 1992], and the Living with Asthma Questionnaire[Hyland]. Quality of life evaluation helps identify the most frequent and troublesome problems. It also demonstrates how the disease interferes with daily life. The questionnaires are likely to be sensitive to changes over time, and the questions have clear relevance to the patient population.

A disadvantage of disease-specific instruments is that they do not allow for comparisons between patients with different conditions.

In general, patients with mild asthma have a better asthma-specific HRQoL than patients with more severe asthma [Erickson et al.; Sanjuas et al.]. However, a large proportion of patients with mild asthma have a poor HRQoL.

In a study from Scotland, quality of life was assessed in 396 adult patients with mild asthma. The patients were 16 to 52 years of age and in the care of family physicians. Their mean FEV_1 was 87% of predicted and PEF was 85% of predicted value. They completed three quality of life questionnaires: the SF-36, SF-12 and St. George's Respiratory Questionnaire (SGRQ). Forty-one per cent reported respiratory symptoms every week in the month before the interview. The presence of any respiratory symptoms in the month before the interview was related to significantly lower quality of life scores on several of the SF-36 scales. Physician contact due to asthma in the 12 months after interview was significantly related to SF-36, SF-12 and SGRQ scores. However, when adjusted for symptoms at the time of the interview, only SGRQ scales remained significant predictors of prospective physician contact [Osman et al.]. In another study of 399 children, quality of life scores were correlated with child-reported anxiety incidence. The children participating in the study had mild asthma symptoms during the two weeks prior to their 12-month follow-up clinical visits. They reported a generally positive quality of life, suggesting that mild-to-moderate asthma does not significantly impair the patient's well-being. Children's responses were strongly influenced by anxiety, regardless of whether anxiety was directly attributed to their asthma [Annett et al.].

Viramontes**,** *et al*, found that most SF-36 scores were higher for patients with mild asthma than for patients with severe disease, with the exception of the emotional role and mental scores which were worse in patients with mild asthma [Viramontes et al.].

Chapman claims that patients' quality of life is likely to be a reflection of actual impairment compared to patient expectations. Patients who regard themselves as having mild disease are likely to have expectations of unimpaired QoL. Another possible explanation for the minimal difference in HRQoL among severity groups would be inadequacy of the instruments used to measure HRQoL [Chapman, 2005].

In another study, 160 adolescent athletes with asthma, allergic rhinitis or exercise induced asthma answered a generic HRQoL-questionnaire. Athletes with a prior diagnosis of asthma had a lower HRQoL scale summary score and lower physical functioning, emotional functioning, and school functioning domain score in comparison to adolescent athletes with no prior diagnosis of these disorders [Hallstrand et al.].

Many patients perceive their asthma as mild or very mild [Erickson et al.; Rabe et al., 2004]. Impaired HRQoL can be inferred by improvement observed even in mild asthma by appropriate therapy [Kauppinen et al.; Koskela et al.; Vermetten et al.].

Some authors have recommended the use of a combination of generic and specific instruments. The two kinds of measuring are likely to produce supplementary information, detecting unexpected positive and negative effects of treatment.

Influence of psychological status on symptoms and asthma-related Quality of Life

There is data indicating that the reporting of symptoms is influenced by psychological status. In a study of 230 outpatients, it was shown that patients with more depressive symptoms reported worse HRQoL, (AQLQ), than asthma patients with similar disease activity but less depressive symptoms. The rate of depressive symptoms was notable, with 45% of the patients enrolled from their primary care practice scoring over the threshold considered positive for depression screening, according to the Geriatric Depression Scale (GDS) [Mancuso et al.]. In a study of 715 subjects, who participated in the European Commission Respiratory Health Survey, a significant correlation was found between anxiety, depression and the report of asthma symptoms [Janson et al.]. In another study by Dales and colleagues, 600 "healthy" individuals were surveyed regarding respiratory symptoms, such as breathlessness and wheezing. Individuals with more depressive symptoms reported more respiratory symptoms [Dales].

Application to clinical practice

The quality of life questionnaires were originally developed and validated for use in clinical trials [Hyland; Jones et al., 1991; Juniper et al., 1993; Marks et al., 1992; Marks et al., 1993]. Those questionnaires have clearly indicated responsiveness to treatment with anti-asthmatic drugs [Juniper et al., 1995; Juniper et al., 1999 d; Juniper et al., 1999 e; Rutten-van Molken et al.]. To be suitable for evaluating disease management in primary health care, questionnaires must be easy to use and validated in that particular setting. The original questionnaires are long, take at least 10 minutes to complete, and are often complex to administer and to score. The HRQoL instruments are not mainly validated for use on individual patients. Simple questionnaires for measurements of health related quality of life would be valuable for surveys of asthma management and for research on asthma in primary care, but might also be used in the management of individual patients. However, several standards need to be met for use of QoL-questionnaires at the individual level. First, they should be easy to administer, score and interpret. Second, they should include a variety of health concepts. Third, floor and ceiling effects should be minimal in order to minimize the numbers of patients who get the lowest or highest scores. Fourth, the scores should have small standard errors, indicating precision for cross-sectional assessments and longitudinal monitoring. Fifth, they should be valid indicators of what ever construct they represent and be sensitive to clinical changes [McHorney et al.].

Almost no studies have examined the utility of health-status measurements in a routine practice of primary care. In a study from the Netherlands, fourteen general practitioners at six general practices monitored 175 patients, aged 18 years or older, having asthma and COPD. Directly before each follow-up consultation, patients completed a self-reporting questionnaire with 27 items. General Practitioners reviewed the questionnaire scores during consultation and recorded their diagnostic and therapeutic interventions. The relationships between patients' quality of life and medication prescription by GPs', smoking cessation devices, patient education and counselling were analysed. There were links between quality of life score and GP intervention. Reports of physical complaints were related to changes in medication and to more education about the control regimen. Emotional complaints were associated with more counselling and extra follow-up appointments. The age of a patient was strongly related to education: the older the patient, the less education supplied. The large majority of GP's had found the information regarding physical complaints useful and more than half of them regarded the other information favourably. The patients had greatly appreciated the personal monitoring; 92-96% enjoyed completing the quality of life questionnaire, which was not taken as time-consuming, and they were also prepared to continue answering the questionnaire in the

future. The majority of GPs were favourable to the contents of the questionnaire and its usefulness. However, they were reluctant to continue this personal monitoring procedure after the experiment [Jacobs et al.].

In a study from Wales, 42 children responded to a quality of life questionnaire. The participants attended four consecutive asthma clinics of which one was a paediatric hospital asthma clinic and the other three were dedicated primary care, nurse-run asthma clinics. The doctor or nurse with the best recent knowledge of a child provided an assessment of asthma control. Any clinical information available could be taken into consideration when making this judgment, including that derived from interview that day. However, the clinicians had no knowledge of the details of the quality of life questionnaires. The parents completed a questionnaire in which they measured the difficulties they experienced as a result of their child's asthma. There was no correlation between overall QoL scores of the children and the assessment of overall asthma control provided by their medical attendants ($r=0.02$, $p=0.98$). There was poor correlation between overall scores of the children and QoL scores of the parent ($r=0.19$, $p=0.18$), as well as between the activity domain scores of children and parents ($r=0.01$, $p=0.45$) [Williams et al.].

In one study, the use of quality of life data in clinical practice was investigated. Approximately 80% of 154 oncologists believed that QoL data should be collected prior to the commencement of treatment, but less than 50% actually did so. Similarly, less than 50% assessed QoL as a method of monitoring the response to treatment, even when the treatment goal was palliation. Given an appropriate instrument the majority believed that QoL data could be collected on a routine basis [Morris et al.].

Relation between Quality of Life and clinical measurement

Most conventional clinical measurement of asthma control, like airway calibre, symptoms, airway responsiveness and asthma severity, assesses the status of the airways. There is convincing data indicating a weak relationship between lung function and quality of life [Juniper et al., 2004] and suggesting that quality of life cannot be inferred from clinical measurement. HRQoL thus has to be measured directly. Certainly, patients with more severe asthma tend to have a reduced quality of life compared to patients with milder disease [Juniper et al., 1992]. Therefore, to get a more complete picture of a patient's status, quality of life should be measured together with the conventional clinical indexes.

Lung function

Uncontrolled asthma is recognized by recurrent episodes of airflow limitation which is usually reversible, either spontaneously or with treatment. There are several reasons for these recurrent episodes of airflow limitation. Many stimuli can cause acute bronchoconstriction, such as allergens, exercise, cold air, fumes, chemicals and strong emotional expressions like weeping or laughing. Acute bronchoconstriction is usually relieved by inhalation from a bronchodilator, e.g., a short-acting β_2-agonist [GINA]. Airflow limitation is also caused by swelling of the airway mucosa, chronic mucus plug formation and airway wall remodelling [GINA]. Measurement of lung function, particularly the reversibility of lung function abnormality, provides a direct assessment of airflow limitation.
Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are directly related to the luminal size of the airway (airway calibre) and the elastic properties of the surrounding lung tissue. Predicted values for FEV_1 and FVC, based on age, gender and height,

have been obtained from population studies. The lower cut-off limit for normal FEV_1 and FVC is usually set at 80% of the predicted value [ATS, 1991; Miller et al.; Pellegrino et al.]. In studies I and II we chose an arbitrary cut-off level of 75% of predicted value to clearly distinguish between patients with normal, and patients with reduced, lung function [ATS, 1991; Miller et al.]. In our studies reference values by Hedenström, *et al*, were used. [Hedenström et al., 1985; Hedenström et al., 1986].

Reversibility

In order to reveal airway obstruction, a reversibility test was performed. Lung function, e.g., FEV_1, was measured before and after inhalation of a bronchodilating drug. In our studies, we have used a combination of salbutamol (5.0 mg) and ipratropium bromide (0.5 mg) inhaled by the use of a jet nebulizer (Aiolos, Medicinsk Teknik AB, Karlstad, Sweden), and lung function was measured before inhalation and 20 minutes after. A 12% improvement in FEV_1, after a bronchodilator, or in response to a glucocorticosteroid therapy, favours the asthma diagnosis [ATS, 1991].
In study III a significant reversibility was defined by an increase in $FEV_1 \geq 10\%$ of the pre-inhalation value. This is in accordance with ATS guidelines where an increase in $FEV_1 < 8\%$ is regarded as within measurement variability [ATS, 1991; Miller et al.].

Peak Expiratory Flow (PEF)

Measurement of peak expiratory flow (PEF) is useful at the clinic or in a primary health care setting to help in diagnosing asthma. An improvement of at least 15%, after inhalation of a bronchodilator or in response to a trial of glucocorticosteroid therapy, favours the asthma diagnosis [Quanjer et al.]. Patients can use the PEF-meter at home for day-to-day monitoring of asthma. However, most patients prefer to adjust treatment based on symptoms rather than on PEF monitoring [Caress et al.]. It has been demonstrated that many asthma patients are reluctant to measure PEF on a regular basis [Cote et al.; Verschelden et al.]. In the AIRE study it was found that ownership of a peak flow meter was the highest in the United Kingdom (40%), but regular use was extremely low in all regions [Rabe et al., 2004].

Asthma is an inflammatory disease

Previously it was assumed that asthma was caused by abnormal contractility of the airway smooth muscle, giving rise to variable airflow obstruction and the common symptoms of wheezing and shortness of breath. Our view of asthma has changed with recognition of the fact that a chronic condition underlies the clinical syndrome. It is well known that patients who die from asthma attacks have an intense airway inflammation. The airway wall is oedematous and infiltrated with inflammatory cells, predominantly eosinophils and lymfocytes. The chronic inflammation leads to enhanced airway hyperresponsiveness with increased asthmatic symptoms. These episodes are usually associated with reversible airway obstruction [GINA]. Asthma is considered to be caused by chronic airway inflammation, and in research there has been a great interest in monitoring biological markers in order to assess the inflammatory process. For clinicians, it would be extremely useful to have reliable, objective methods on which to base clinical decisions. It has been claimed that outcomes such as markers of inflammation, including exhaled NO, bronchial responsiveness, reversibility to bronchodilators and lung function, may reflect clinical status in the asthmatic patient.

Exhaled nitric oxide

There is increasing evidence that endogenous nitric oxide (NO) plays a key role in physiological regulation of airway functions involved in airway diseases, including asthma. Nitric oxide is produced in increasing amounts in patients with asthma. Currently more than 1.000 publications about exhaled nitric oxide are published. Gustafsson and colleagues first demonstrated that NO can be detected in the exhaled air of animals and humans [Gustafsson et al.], and Alving and colleagues were the first researchers to report increased levels of exhaled NO with asthma [Alving et al.]. Measurement of the concentration of NO in exhaled air offers a useful non-invasive method of assessing inflammatory airway disease. The level of exhaled NO is not increased during bronchoconstriction unless there is coexisting inflammation. Therefore, exhaled NO may play a part in differentiating between the inflammatory and bronchospastic components of clinical asthma, and may also be useful for guiding the therapeutic use of steroids and other anti-inflammatory agents [Ashutosh].
Increased levels of NO are associated with eosinophilic activity, but the exact role of NO in asthma remains unknown.

A major goal of asthma therapy is to control airway inflammation. Therefore the detection and monitoring of the inflammatory component of asthma is of great clinical importance. Persistent inflammation in asthma has been evaluated by bronchial lavage, bronchial assessment of sputum eosinophilia, bronchial provocation tests to demonstrate bronchial hyperreactivity (BHR) or a clinical assessment based on persistence of symptoms, low FEV_1 and variability of peak expiratory flow. Measurement of exhaled NO has great potential, as a test to assess airway inflammation, because it is easy to perform and convenient for the patient. Widespread clinical use, especially in primary care, however, would require an availability of less expensive and more reliable equipment as well as standardization of techniques and reporting. Establishment of normal ranges, and clarification of the significance of NO value and its therapeutic usefulness, also needs further research and consensus. The diagnostic significance of exhaled NO needs to be evaluated in the context of the overall clinical picture [Ashutosh].

Airway hyperresponsiveness

Airway hyperresponsiveness (AHR) is a characteristic feature of asthma in which the airways respond too easily and too much to various stimuli [Sterk et al.; Crapo et al.]. The potential for excessive narrowing is clinically the most relevant physiological abnormality in asthma. The underlying mechanism of this “hyperresponsiveness” is not known, but it may be related to altered behaviour in airway smooth muscle secondary to changes in its contractility or phenotype [Solway]. Several mechanisms have been proposed to explain this airway hyperresponsiveness, but evidence suggests that inflammation is an important factor.
The most common clinical use of provocation tests, for airway hyperresponsiveness, is for excluding or confirming asthma. If the patient has symptoms indicating asthma, but investigation with spirometry and a reversibility test has failed to confirm the diagnosis, it is relevant to perform a bronchial challenge test. If the test is negative, the asthma diagnosis should be questioned, a positive test supports the asthma diagnosis.

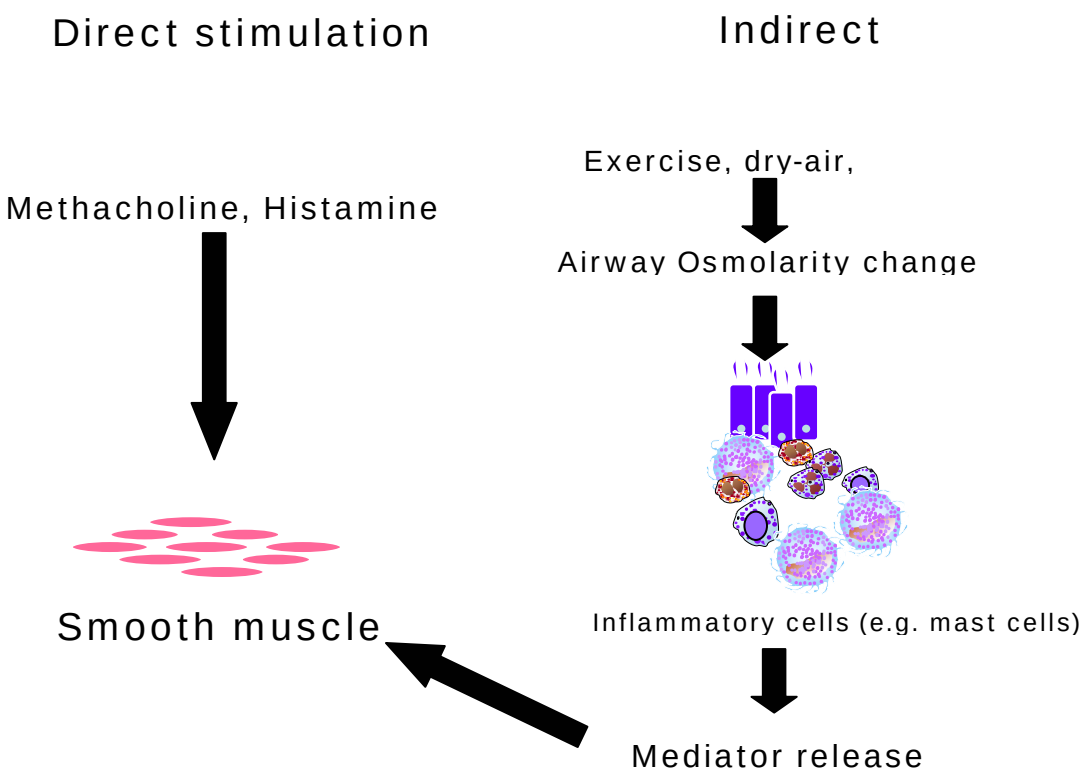

Figure 2. Airway hyperresponsiveness can be caused by stimuli acting directly or indirectly on smooth muscle.

The mechanism of hyperresponsiveness can be classified as causing airflow limitation, directly by stimulating an airway smooth muscle, or indirectly by releasing active substances from mediator-secreting cells, such as mast cells or nonmyelinated sensory neurons. Histamine and methacholine are the two stimuli most used with a direct effect on airway smooth muscles. Other provocative stimuli like exercise, eucapnic voluntary hyperventilation (EVH) of dry air and aerosols of hypertonic saline have no direct effect on smooth muscles. Instead they are assumed to release mediators from nerve endings, mast cells, or other cells in the airways [Sterk et al.; Crapo et al.; Argyros et al.] (Figure 2.).

Airway hyperresponsiveness can be quantified by constructing stimulus-response curves and describing them either in terms of the provocative dose, PD, or provocative concentration, PC, producing a specified fall in lung function. Usually, a fall in FEV_1 of 20% of the pre-test value or the value obtained after inhalation of the diluent, is regarded as a positive test. The provocative concentration or dose that reduces FEV_1 by 20% from the baseline, PC_{20} FEV_1 or PD_{20} FEV_1, thus serves as an index of airway responsiveness.
In an exercise test, stimulus-response curves are not used. Instead a 10% fall in FEV_1 or a 20% fall in PEF from the baseline, 5 to 15 minutes after exercise, have been considered as positive [Sterk et al.; ATS, 2000, Holzer et al.].

The mechanism of bronchoconstriction induced by hyperventilation with cold or dry air is not clear to us. Evaporation of water from the respiratory mucosa as well as conditioning of the inspired air by the respiratory mucosa, is involved in the process [Anderson et al.; Postma et al.].

In a eucapnic dry air provocation test FEV_1 is performed at 1, 3, 5, 10 and 20 minutes after 4-6 minutes of hyperventilation of dry air [Argyros et al.]. Hyperresponsiveness is defined as a post-challenge fall in FEV_1 >10% compared with pre-challenge value [Anderson et al.]. The symptoms provoked by eucapnic voluntary hyperventilation (EVH), such as coughing, chest tightness, dyspnoea and wheezing are identical to those following exercise. The major advantage in using EVH instead of exercise is the ability of the subject with ease to achieve and sustain a higher ventilation rate than that which could be obtained during exercise [Holzer et al.]. Eucapnic voluntary hyperventilation has a high specificity for active asthma: 90% when a fall in FEV_1 of 10% is taken as abnormal, and 100% when a 15% fall is considered abnormal [Hurwitz et al.].

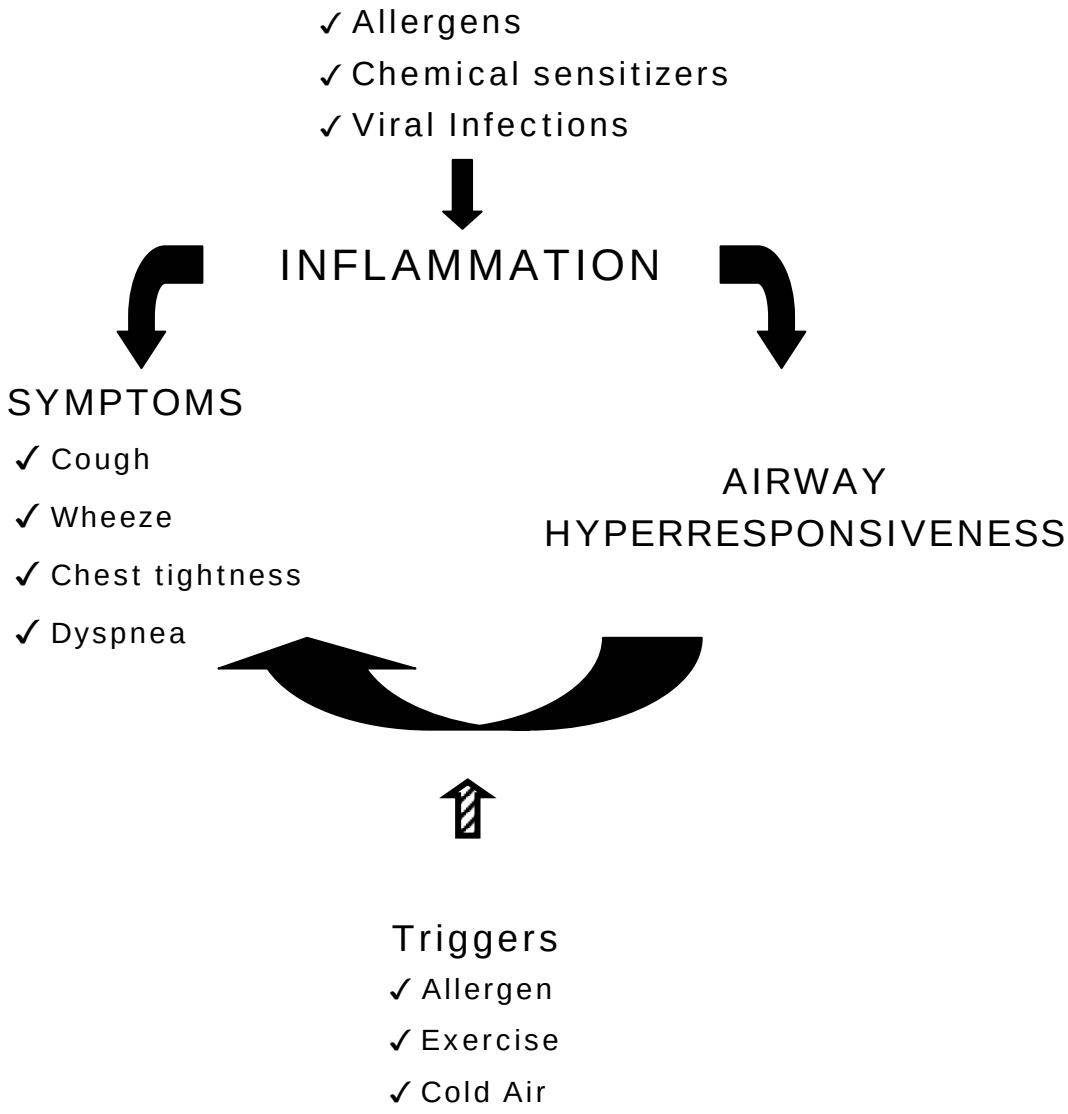

Figure 3. Asthma is an inflammatory disease that leads to airway hyperresponsiveness and asthma symptoms.

Early treatment with inhaled corticosteroids in asthma

Early treatment with corticosteroids is recommended in guidelines for treatment of patients with mild asthma when inhaled bronchodilators alone are insufficient to control the disease [GINA; NAEPP]. Since a majority of patients have mild asthma, determining the appropriate circumstances for initiating treatment, with inhaled corticosteroids, is an issue of major

importance in asthma care [Drazen et al.]. Most specialists agree that patients with occasional symptoms can be effectively treated with inhaled β_2-agonists alone. If this treatment is insufficient, inhaled corticosteroids should be added. The problem with this approach however, is, that the patients have to experience symptoms before progressing to the next step in treatment. Therefore, some specialists have advocated the use of inhaled corticosteroids as first-line therapy for most patients with asthma [Strube et al.]. They argue that, although a β-agonist offers temporary clinical improvement, an underlying inflammation persists. It has been shown that patients taking inhaled corticosteroids had better symptom control and required fewer supplementary drugs. In addition, bronchial hyperresponsiveness was reduced and lung function preserved [Haahtela et al., 1994; Agertoft et al.; Selroos et al., 1995]. As airway inflammation is present also in patients with very mild asthma, there may be a risk of irreversible airflow obstruction due to structural changes (remodelling) of the airway wall. These structural changes are correlated with the duration of the disease [Redington et al.; Selroos et al., 2004]. Early treatment is associated with a more favourable long time lung function outcome than if treatment is started after a delay of some years [Agertoft et al.;Zeiger et al.;Peat et al.,Lange et al.;Haahtela et al.,1991, Haahtela et al.,1994; Haahtela 1999; Selroos et al., 1995; Selroos et al., 2004;Pauwels et al.]. Because steroids are effective anti-inflammatory drugs, it is possible that early treatment with steroids may prevent the development of irreversible changes and subsequent progression towards a more severe disease. There are, however, reasons for not prescribing steroids to all patients with newly diagnosed asthma. Steroids are not beneficial to all patients, and corticosteroid treatment entails a risk of side effects, especially in long-term treatment. Although there are only few long-term studies, on the outcome of mild asthma, no clear indications have appeared that adult asthma patients with mild disease are at risk of progression towards crippling, obstructive lung disease [Drazen et al.].

AIMS

The general aims of this thesis have been to assess quality of life in patients, preferably with mild asthma, and to elucidate whether or not there is a relationship between quality of life and lung function, bronchial responsiveness and markers of inflammation.

The specific aims:

– To estimate and describe quality of life in patients with asthma attending a primary health care unit, and using a disease-specific questionnaire;

– To find out whether or not there is any relationship between quality of life and lung function and between quality of life and the response to a simple question regarding symptoms;

– To investigate the relationship between quality of life and markers of asthma such as reversibility to a bronchodilator, bronchial responsiveness to direct and indirect stimuli, and exhaled nitrogen oxide;

– To investigate if quality of life and markers of asthma in patients with mild asthma, are influenced by treatment with an inhaled steroid;

– To evaluate if change of treatment will influence quality of life in patients with mild asthma and with a poor perception of symptoms.

Materials and methods

Methods are described in detail in my publications and are briefly summarised below. All studies were approved by the local Ethic Committee.

Subjects

All patients, 18-65 years of age, had previously attended one of four primary health care centres on the island of Södermalm, an inner-city part of Stockholm with approximately 100. 000 inhabitants. All patients had experienced symptoms interpreted by a general practitioner to be asthmatic. These patients were identified in the primary care asthma register and then invited by mail, where they were asked whether or not they wished to participate in the study. Thus, none was included in connection with a consultation due to worsening asthma symptoms. Patients were excluded if they were pregnant or if they suffered from serious disorders, such as psychiatric disease, alcoholism, rheumatic arthritis, cancer or COPD. Since our intention was to study a population of primary care patients with mild asthma, smokers and ex-smokers were not excluded as long as they had no clear indication of COPD.
In studies III and IV, patients were only included if they had not been treated with inhaled steroids during the previous three months and considered themselves free of symptoms as assessed by the visual analogue scale (VAS).
The 42 patients who participated in study II were all recruited from the 120 patients who participated in study I. All 70 patients in study IV were recruited from the 77 patients who participated in study III.

Study design

Study I

The patients (n=120) answered a postal questionnaire regarding heredity, allergic symptoms, smoking habits and medication and were examined at the primary care centre. They indicated the impact of their disease on a VAS, (see below), after which a lung-function test was performed before and after bronchodilatation. They also answered a quality of life questionnaire (AQLQ).

Study II

In 20 patients who considered themselves to be symptom-free (VAS≤20 mm) and who had a reduced lung function (FEV_1≤75% of predicted value), medication was increased during three months according to a fixed schedule. Twenty-two patients who also experienced few symptoms (VAS≤20 mm), but who had normal lung function (FEV_1>75% of predicted value), served as a control group. In this group, treatment was unchanged. After three months, all measurements, except for the postal questionnaire, were repeated.

Study III

From 77 patients who considered themselves free or almost free of symptoms (VAS ≤30 mm), according to the same question as in studies I and II, exhaled nitric oxide (NO) was analysed, and blood samples for analysis of specific IgE were drawn. In addition, spirometry and

reversibility test were performed. Airway responsiveness was assessed by a bronchial methacholine challenge, and eucapnic hyperventilation with dry air was performed in random order at two further visits. All three visits took place within 10 days.

Study IV

Seventy out of 77 patients who participated in study III agreed to participate in study IV. The patients were randomized for either three months of treatment with inhaled fluticasone propionate (250µg bid) or a placebo. After the treatment period, all tests described in study III were repeated, identical to the pre-treatment procedure.

Methods

Postal questionnaire

Before their first visit to the health care centre, each of the patients had received a postal questionnaire. The questionnaire included questions about asthma, allergic rhinitis, chronic bronchitis, COPD and questions on respiratory symptoms. Questions concerning any family history of asthma and chronic bronchitis/emphysema, use of asthma medicines, smoking habits, socioeconomic groups and professions were also included. The questionnaire has been used in the OLIN-studies in northern Sweden [Lundbäck et al., 1991, Lundbäck et al., 1993; Rönmark].

Visual Analogue Scale (VAS)

The idea in all studies was to get an impression of the patients' own opinions of their asthma status in a situation similar to the routines in a primary care unit. The patients were asked to indicate their symptoms during the last two weeks on a visual analogue scale (VAS). We used a VAS as a horizontal line, 100 mm in length, anchored by world descriptors at each end. The patients indicated the severity of their asthma symptoms by answering the question: "Have you experienced any asthma problems or breathing difficulties during the last two weeks?" Each end of the scale indicates the range being considered, from "no problems at all" to "problems so bad that I had to be admitted to hospital".

Quality of Life

In all four studies we used the Asthma Quality of Life Questionnaire (AQLQ) previously described in detail. The questionnaire has been validated in several studies, has been shown to have good measurement properties and is the most used quality of life questionnaire in asthma research.

Lung function

Lung function was measured with a Micro-Lab 3300 Spirometer (Micro Medical Ltd, Rochester, Kent, UK.) according to the standards of the American Thoracic Society [ATS, 1991]. Reference values by Hedenström *et al*. were used [Hedenström et al., 1985; Hedenström et al., 1986]. For reversibility tests, salbutamol (5.0 mg) and ipratropium bromide (0.5 mg) was mixed and inhaled using a jet nebulizer (Ailos, Medicinsk Teknik AB, Karlstad, Sweden). Lung function was measured 20 minutes after inhalation. In studies III and IV, significant reversibility was defined as an increase in $FEV_1 \geq 10\%$ of the pre-inhalation value, which is in accordance with the American Thoracic Society (ATS) guidelines, where an increase <8% of pre-inhalation values, is likely to be within measurement variability [ATS, 1991].

Bronchial provocation tests

Methacholine provocation test

In studies III and IV bronchial responsiveness to methacholine was assessed by a provocation test using a wedge Spirometer (Vitalograph, Buckingham, UK). Inhalation of the diluent was followed by inhalation of doubled concentrations of methacholine, starting at 0.5 mg/mL. The challenge was stopped when FEV_1 had decreased by 20% compared to the value obtained after inhalation of the diluent, or after inhalation of the highest methacholine concentration (32 mg/mL). The results were expressed as the cumulative dose or concentration of methacholine, causing a 20% decrease in FEV_1 ($PD_{20}FEV_1$ and $PC_{20}FEV_1$) and a dose-response slope (DRS), i.e. the percentage decrease of FEV_1 as a function of the cumulative dose (mg), calculated by linear regression [Malmberg et al.; Sterk et al.].
Reference values for bronchial responsiveness to methacholine have been defined in our laboratory. Reference values for $PD_{20}FEV_1$ and $PC_{20}FEV_1$, and the DRS were obtained in 203 healthy and 102 asthmatic subjects. The cut-off level for bronchial hyperresponsiveness was defined as based on the distribution of log $PD_{20}FEV_1$ for healthy and asthmatic subjects. The cut-off level was set at the point were the two distributions met, and was found to be 0.56 mg, corresponding to the 15th percentile of the distribution of the healthy subjects and the 80th percentile for the group of asthmatic subjects (Figure 4). The method is described in detail in study III.

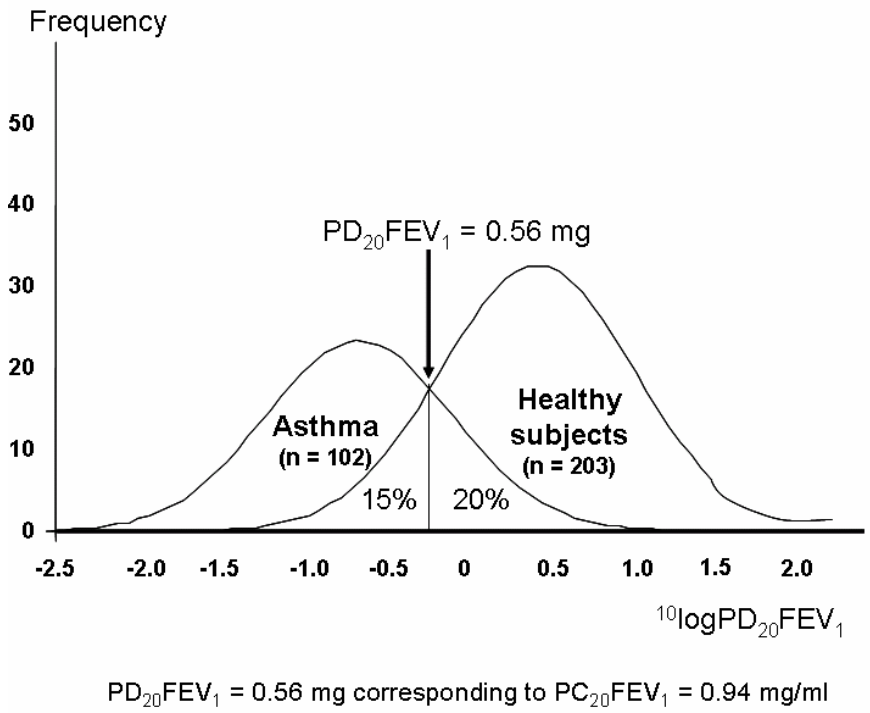

Figure 4. The distribution of bronchial responsiveness to methacholine in 203 healthy and 102 asthmatic subjects. The cut-off line for normal bronchial responsiveness has been defined as the point where the two distributions meet. This yields a $PD_{20}FEV_1$ of 0.56 mg, which corresponds to the 15th percentile in the healthy subjects and the 80th percentile in the asthmatic subjects. Study III.

Eucapnic dry air provocation test

Eucapnic hyperventilation was performed for four minutes with dry air containing 5% CO_2 at room temperature. (Ailos asthma test®, Karlstad, Sweden). The target ventilation was $35xFEV_1x0.75$, which was adjusted by the patient breathing through a balloon, and FEV_1 was measured 1, 3, 5, 10, 15 and 20 minutes after the hyperventilation. The maximal FEV_1 decrease compared to the baseline, pre-hyperventilation value was recorded [Argyros et al.]. A post-challenge fall in FEV_1 >10% was defined as positive [Anderson et al.].

Exhaled nitrogen oxide

Nitric oxide levels were measured by chemiluminiscense following a reaction with ozone (NIOX®, Aerocrine, Stockholm, Sweden). Exhaled NO was determined during a single breath exhalation. The measurements were performed in accordance with recommendations from the American Thoracic Society [ATS, 1999], with an exhalation flow rate of approximately 50mL/s. To decrease contamination from the oral cavity, subjects were asked to rinse their mouths with water and sodium bicarbonate (10%) for one minute prior to the measurement procedure. A NO-concentration below 20 ppb was considered normal.

Atopy

Atopy was assessed by measurement of specific IgE antibodies in plasma (Phadiatop (Unicap®, Pharmacia, Uppsala, Sweden). IgE values ≤ 0.35 were considered normal.

Statistics

Results are presented as mean values with a 95% confidence interval (95% CI) or (SEM) when data was distributed normally, or median (25^{th}-75^{th} percentiles) when data were not normally distributed. Correction for multiple comparisons was performed using the Bonferroni method when appropriate ($p<0.01$). Comparisons were performed by analysis of variance (ANOVA) with Fishers post hoc test, Student's t-test for paired and unpaired observations, linear regression and Pearson's correlation coefficient, when data was distributed normally. For data, not distributed normally, the Mann-Whitney U-test was used for independent comparisons and the Wilcoxon signed rank test for dependent comparisons. A p-value <0.05 was considered statistically significant.

Results

Patients' characteristics

Study	Group	Number	Sex % F	Mean age	FEV_1 % predicted	Smoker %	Ex-smoker %	Non-smoker %
I	Total	120	60	40	79.0	36	27	37
	A	50	58	36	89.7	16	28	56
	B	25	44	46	66.0	56	28	16
	C	24	75	42	87.1	42	25	33
	D	21	66	43	59.6	52	29	19
II	Total	42	53					
	A	22	55	35	88.9	4	32	64
	B	20	50	47	66.3	55	30	15
III	Total	77	66	38	90.6	25	26	49
IV	Total	70	70			26	27	47
	FP	36	75	38	88	33	28	39
	Plac	34	65	39	92	18	26	56

Table 1. Patients' characteristics in studies I-IV. F=female, FP=Fluticasone propionate, Plac=Placebo.

Quality of Life

Study	Group	Number	QoL score	MID >0.5, %
I	A	50	6.0	
	B	25	5.4	
	C	24	4.8	
	D	21	4.6	
II	A	22	≈6.0	27
	B	20	≈5.4	55
III	Total	77	5.75	
	Atopic	53	5.88	
	Non-atopic	20	5.42	
IV	FP	36	5.62	42
	Plac	34	5.74	38

Table 2. Patients' characteristics in studies I-IV. Mean quality of life overall score at first visit as assessed by AQLQ. In the intervenient studies II and IV, the percentage of patients that reached the minimal important difference, MID, is shown. FP=Fluticasone propionate, Plac=Placebo.

Study I

The 120 patients were categorized into four groups according to a question regarding their symptoms on a VAS, and according to lung function.

	FEV_1 >75%	**FEV_1 ≤75%**
VAS 0-20 mm	**A**	**B**
VAS >20 mm	**C**	**D**

Table 3. Patients in studies I and II divided into groups according to VAS and pre-bronchodilator FEV_1.

Patients who indicated few symptoms (VAS<20 mm) and who had normal lung function (group A) had a higher quality of life score (6.0) than patients in the other groups. Patients in group B, who also indicated few symptoms, and had reduced lung function, had a statistically significant lower quality of life score overall (5.4) than patients in group A. Patients in groups C and D who indicated more symptoms (VAS>20 mm) had lower quality of life scores than the other groups (4.8 and 4.6). In spite of the fact that there was a difference in lung function between group C and D, we found no statistically significant difference in quality of life between the groups. For environmental factors, like exposure to cigarette smoke, dust, air pollution and strong odors there was a clear difference between patients who experienced symptoms (groups C and D) and those who did not (groups A and B).

There was a fairly good correlation between VAS and quality of life ($p<0.001$ for all domains), whereas the correlation between FEV_1 and quality of life was poor. No significant correlation was found between VAS and FEV_1. In general, men had higher quality of life scores than women, with regard to all domains and overall estimation. Patients without steroid treatment had higher quality of life scores than patients who were treated with steroids.

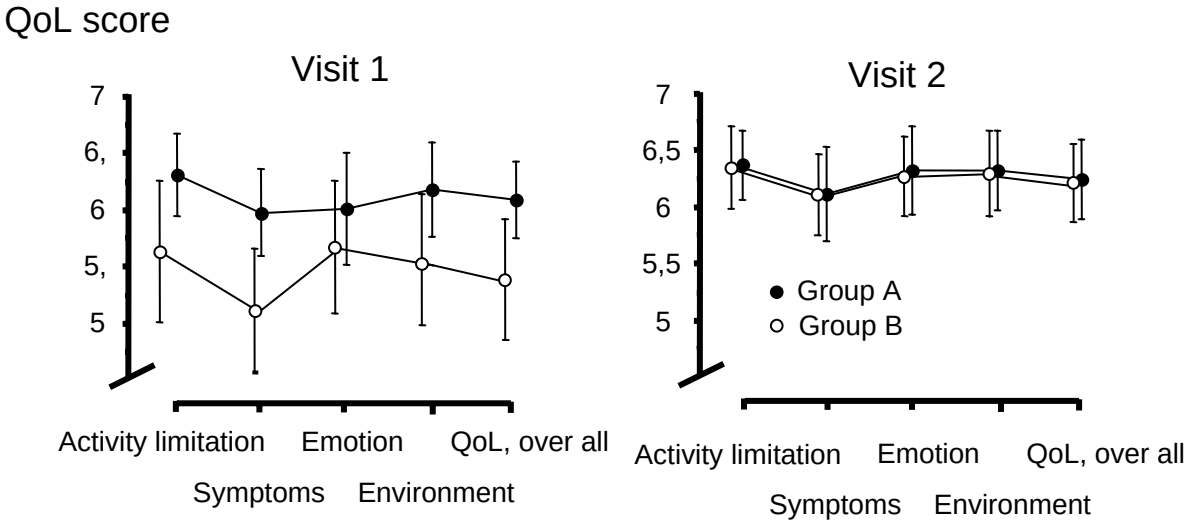

Figure 5. Quality of life score in patients without symptoms with normal (group A) and impaired lung function (group B). Visit 1=study entry; visit 2=data after 3 months of unaltered treatment (group A) or increased treatment (group B). In group B a significant improvement was observed after 3 months (Study II.).

Study II

After three months of increased treatment according to table 4, a significant improvement was observed for all domains and overall assessment in the Asthma Quality of Life Questionnaire, (AQLQ), for patients in group B. In group A, where no alteration of therapy took place, we found no significant change in quality of life. At the second visit we found no difference in quality of life between the two groups (Figure 5.).

	I	II	II
Current therapy	No treatment	≤400µg BUD per day	>400µg BUD per day
	β-Agonist prn	≤400 µg BDP per day	>400 µg BDP per day
	DSCG prn	≤200 µg FP per day	>200 µg FP per day
Intervention	200 µg BUD bid	Doubling of the	Add salmeterol 50µg
	β-Agonist prn	steroid dose	bid

Table 4. In patients with FEV_1 ≤75% of predicted value treatment was added.
BUD: budesonide; BDP: Beclomethasone diproprionate; FP: fluticasone dipropionate; DSGC: disodium cromoglycate.

In group A where there was no change in therapy approximately 25% of the patients reached the minimal important difference MID of 0.5 (6 out of 22). In group B, where treatment was improved, more than 50% reached the MID (12 out of 20). The overall score decreased in eight subjects in group A and in one subjects in group B.

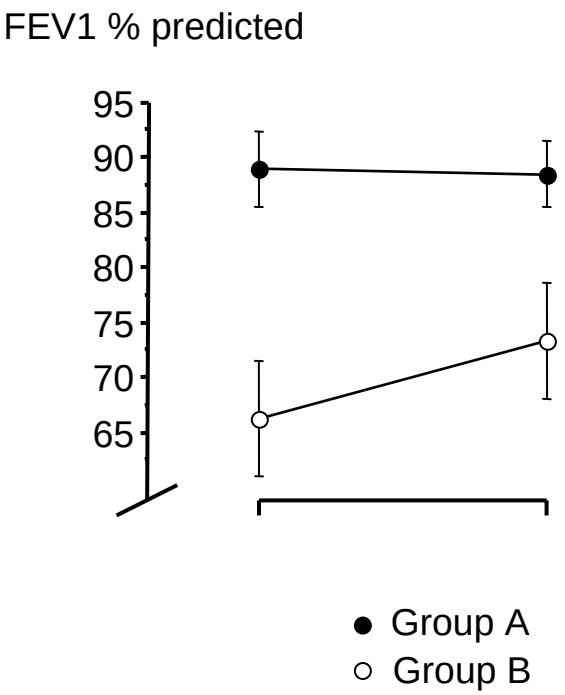

Figure 6. Lung function assessed by FEV_1 before (visit 1) and after (visit 2) 3 months of unaltered treatment (group A) or increased treatment (group B).

Lung function was increased in group B, but not up to the same level as in group A. (Figure 6.) In group B reversibility decreased from 12.3% (1.6%) to 7.2% (1.0%) of predicted value. Corresponding values in group A were 4.0% (1.2%) and 5.0% (1.4%).

Study III

All tests, including methacholine challenge, dry air challenge, levels of exhaled NO and reversibility to a bronchodilator, were normal in 8 of the 77 patients. Four of them had symptoms of asthma according to the AQLQ, and an overall score <5. We can not exclude the possibility that these four subjects suffered from asthma. In the four remaining patients, with all tests negative and high quality of life scores, the asthma diagnosis was probably erroneous.

In 73 out of 77 patients a blood sample for IgE was analysed. 53 of them had a positive and 20 a negative Phadiatop® test.

The mean quality of life scores for the whole group were: activity limitation 6.00, symptoms 5.67, emotion 5.92, environment 5.49 and overall score 5.75. Atopic patients had higher scores than non-atopic. The difference between atopic and non-atopic subjects reached the MID in the activity limitation domain (0.68) and environment domain (0.74) but not in the symptom (0.41) and emotional domains (0.12) (Figure 7.).

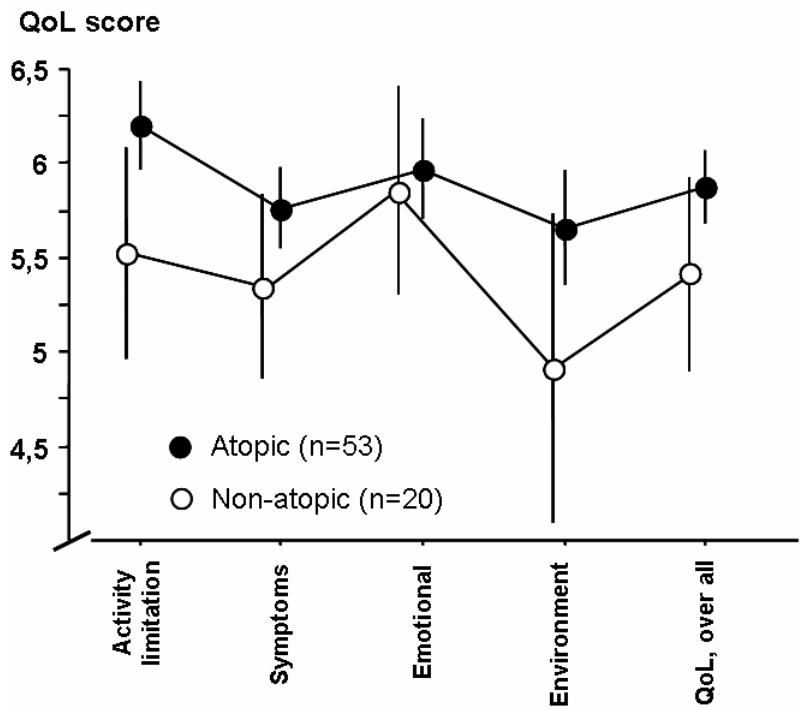

Figure 7. Quality of life (QoL, 4 domains and overall score) in asthmatic subjects with and without atopy. Results are presented as mean values with a 95% confidence interval.

For technical reasons, exhaled NO was measured only in 73 out of 77 patients. The level of exhaled NO was elevated (≥20 ppb) in 37 subjects and normal (<20ppb) in 36 patients. Bronchial challenge, with methacholine and eucapnic hyperventilation, was performed in all 77 subjects, of whom 59 had a positive methacholine test defined as PD_{20} $FEV_1 \leq 0.56$ mg. A post-challenge decrease >10% was found in 24 patients after a eucapnic hyperventilation challenge.

There was no significant correlation between quality of life and any of exhaled NO, lung function, reversibility, and responsiveness to methacholine or dry air.

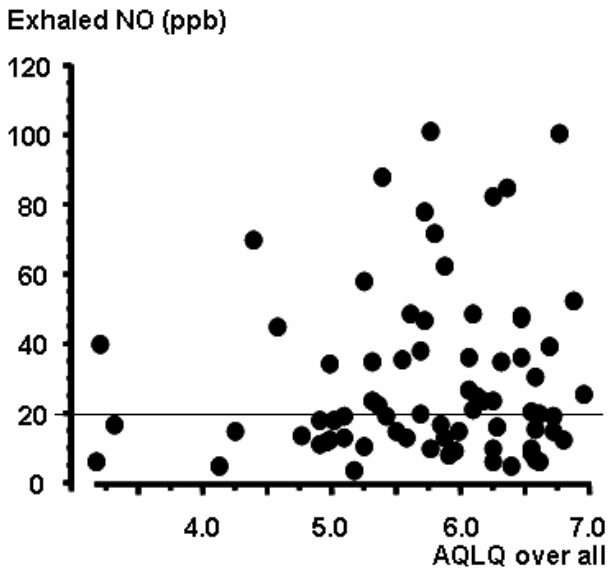

Figure 8. Relationship between quality of life overall score (AQLQ) and exhaled NO (n=73).

The relationship between the quality of life overall score and the level of exhaled NO is shown in figure 8 (n=73). Patients with an increased level of exhaled N0≥20 ppb had significantly

higher quality of life scores in the activity limitation domain (p=0.04) and the environmental domain (p=0.03), compared to patients with normal levels of exhaled NO. For the environmental domain this difference reached the MID.

The difference in the quality of life score, between groups of patients with normal and abnormal bronchial responsiveness to methacholine, dry air, elevated NO in exhaled air and reversibility >10% of the pre-bronchodilator FEV_1, did not in any of the cases reach the minimal important difference (MID) of 0.5.

Levels of exhaled NO did significantly correlate with bronchial responsiveness to methacholine (r= -0.37; p=0.002), and dry air (r= -0.47; p<0.0001). A weak, though significant, correlation was also found between FEV_1 (% of predicted) and reversibility (r= -0.44; p<0.0001). Otherwise no significant correlations were found between the tests. The mean value of exhaled NO was higher in the atopic patients, 32.9 (26.1-39.7) ppb compared to the non-atopic group, 21.0 (10.8-31.2) ppb (p=0.01). There was a tendency toward enhanced bronchial responsiveness to methacholine in the atopic group (PD_{20} FEV_1 0.16 [0.07-0.40] mg) compared to the non-atopic group 0.26 (0.15-0.78) mg, (p=0.066) Bronchial responsiveness to eucapnic hyperventilation was similar in atopic and non-atopic subjects.

Study IV

All seventy patients completed the study. At visit one, the mean quality of life overall score was 5.62 in the fluticasone group (n=36) and 5.74 in the placebo group (n=34). After three months of treatment the scores had increased to 6.00 in both groups (Figure 9.). The increase in quality of life scores was below the minimal important difference, (MID<0.5) in both groups, 0.38 in the fluticasone group and 0.25 in the placebo group.

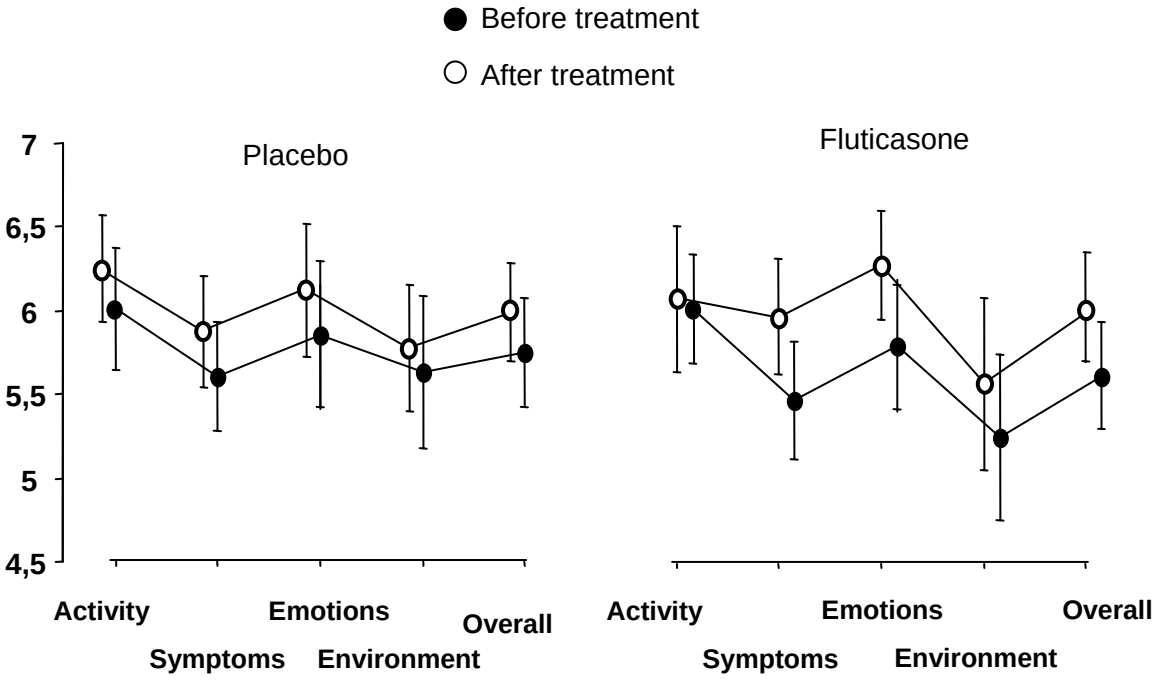

Figure 9. Quality of Life, assessed with the Asthma Quality of Life Questionnaire (AQLQ), for the four domains and overall, before and after three months of treatment in asthma patients inhaling fluticasone (250µg b i d) or placebo. Mean values and 95% confidence interval.

An overall score improvement ≥0.5 of AQLQ was observed in 42% of the patients in the fluticasone group and 38% in the placebo group. There was no significant difference between the fluticasone and the placebo group with regard to change in quality of life.

Due to technical problems, exhaled NO was measured at both visits in only 64 of the 70 patients (33 patients in the fluticasone group and 31 patients in the placebo group). A weak, but statistically significant correlation was found between the decrease of exhaled NO and an improvement in quality of life overall scores in the fluticasone group (r= -0.43, p=0.013). Otherwise no significant correlations were found between changes in quality of life scores and other parameters.

After three months of treatment there was a significant decrease in the level of exhaled NO in the fluticasone group (p=0.0002), from 19.3 (13.3-39.5) ppb before to 13.9 (8.1-18.7) ppb after treatment (Figure 10.). In the placebo group, pre-treatment value was 20.7 (12.8-36.5) ppb and post-treatment value 23.0 (10.5-35.7) ppb (p=0.39). The effect of treatment differed significantly between the groups (p=0.02).

In the 34 (53%) patients with exhaled NO values >20 ppb before treatment a reduction of NO in the fluticasone group, from 39.7 (29.7-72.9) ppb to 16.9 (13.2-28.1) ppb (p=0.008) was observed. Corresponding values in the placebo group were 36.5 (25.5-49.6) ppb and 35.3 (27.5-44.9) ppb (p=0.50). Neither fluticasone nor placebo influenced the level of exhaled NO in those who had normal levels (<20ppb), prior to the treatment period.

After three months of treatment FEV_1 was increased by 2.8% (p=0.02) in the fluticasone group and 0.8% (p=0.53) in the placebo group. The change in FEV_1 differed significantly between the groups (p=0.03). Corresponding values for FVC was 0.8% (p=0.19) in the fluticasone group and 1.1% in the placebo group (p=0.82 between groups).

Reversibility was 7.6 (5.3-9.9) % in the fluticasone group before treatment. After three months of treatment, the reversibility was 6.7 (4.9-8.5) %. The corresponding values in the placebo group were 6.1(4.3-8.0) % and 6.8(4.6-9.0) %, respectively.

A bronchial methacholine challenge was performed in all 70 patients at both visits. In the fluticasone group the median $PD_{20}FEV_1$ increased from 0.18 (0.07-0.57) before to 0.42 (0.16-0.80) after, treatment (p=0.09). In the placebo group the corresponding values were 0.22 (0.10-0.50) before and 0.25 (0.14-0.52) after treatment (p=0.36). The change of bronchial responsiveness induced by treatment did not differ significantly between the groups (p=0.5).

Pre- and post-treatment eucapnic hyperventilation challenges were performed on all 70 patients. In the fluticasone group there was a significant reduction in the post-challenge decrease from 10.6 (7.5-13.7) % to 6.4 (4.2-8.6) % (p=0.005). In the placebo group the corresponding values were 7.0 (4.2-9.8) % before and 7.2 (3.8-10.6) % after treatment (p=0.61). The difference between the groups was significant (p=0.02).

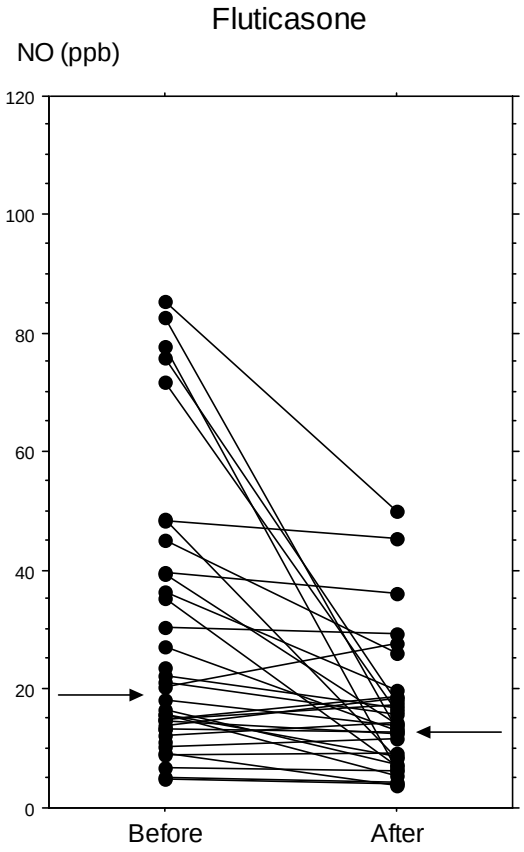

Figure 10. Levels of exhaled NO before and after treatment with fluticasone. Each line represents one patient. Arrows indicate median values. A significant decrease was observed in the fluticasone group (p=0.0002).

Discussion

The aims of these studies have been to focus on patients with mild asthma who had visited a primary care centre. Prior to the studies all patients had experienced symptoms interpreted by a general practitioner to be asthmatic. From previous studies, it is apparent that most asthmatic patients visiting a primary care unit suffer from mild disease [Rabe et al., 2004; Ställberg et al.]. In the worldwide AIRE-study of adult patients identified by telephone screening of households, 63% of patients in Western Europe and 59% in the United States had mild persistent or intermittent asthma based on the severity classification in GINA guidelines [Rabe et al., 2004; GINA]. In a Swedish primary care study, 26% of the patients were completely or almost free of symptoms and 59% had symptoms "sometimes". Two thirds of the asthmatics classified their asthma as mild or very mild [Ställberg et al.]. These studies clearly indicate that a substantial number of the asthmatic patients in primary care suffer from mild disease. We therefore focused our studies on this group of patients with mild asthma, a group of patients that has not previously been extensively studied.

Asthma severity

The idea in the present studies was to get an impression of the patients´ opinion of their asthma status in a situation similar to the routines in a primary care unit. Therefore, all subjects were categorized according to their response to the question "Have you experienced any asthma problems or breathing difficulties during the last two weeks?" on a visual analogue scale (VAS). As there is no generally accepted cut-off limit for discriminating between mild and moderate asthma symptoms on the VAS, and the aim was to identify patients with no symptoms or very mild ones, an arbitrary cut-off limit of 20 mm was chosen in studies I and II. In studies III and IV we wanted to study the relationship between quality of life and "objective" measures of asthma and we therefore chose a slightly higher cut-off level (30 mm), based on the assumption that the "objective" measures probably are closer to normal in patients with VAS-score ≤20 mm.

A disadvantage in choosing these criteria is that our results are not directly comparable with other studies where guidelines have been used for severity classification. In the AIRE-study, and in the study by Ställberg *et al* GINA-classification was used to classify patients. However in both studies there was a clear difference between the patients´ own perceptions of asthma control and reported symptom severity. Worldwide, asthma-patients tend to overestimate control and underestimate severity, suggesting a willingness to accept symptoms and lifestyle limitations [Rabe et al., 2004; Ställberg et al.]. In a primary care study in Belgium, it was obvious that general practitioners tended to assess asthma severity based on daytime symptoms rather than adhering to GINA guidelines [Verleden et al.].
The AIRE-study showed that lung function tests were not frequently used. With the exception of Central and Eastern Europe, more than 50% of asthmatic patients reported never having performed a lung function test, and only one in three had performed a lung function test during the previous year. Ownership of peak flow meters was the most frequent in the United Kingdom (40%) but regular use was very low in all regions [Rabe et al., 2000].

Correlation between Quality of Life and clinical measures

In study I we examined asthma patients with asthma of varying severity and found that quality of life differed between the groups. In general, patients with few symptoms and normal lung function had higher quality of life scores, compared to patients who experienced more symptoms and impaired lung function. However, the correlation between quality of life and lung function, as assessed by FEV_1, was weak. It is evident that the correlation is weak between lung function and how patients feel and function in daily activities. One explanation would probably be that patients are different with regard to physical activities. An active person in a high-pressure job, who also is an athlete, is probably more bothered by airway obstruction than a more laid-back person who works at home and who can easily regulate his/her life to avoid situations that trigger asthma symptoms. Although both patients present similar degrees of airway narrowing, the active person is likely to have a much greater impairment in quality of life [Juniper, 1997]. Another explanation could be that lung function only reflects the situation at the time of measurement, while the AQLQ score indicate the patient's discomfort during the last two weeks.
There are a number of studies showing that correlation normally is weak between lung function and quality of life [Juniper et al., 1993; Rutten-van Molken et al.; Rowe et al.; Leidy et al.].

In study I, the most striking difference between patients who, experienced symptoms according to the VAS, and those who did not, was in the environment domain in the quality of life

questionnaire. This finding suggests that airway responsiveness to irritating stimuli is more closely related to patients´ experiences of symptoms and quality of life than lung function as assessed by spirometry. Therefore, in study III, we wanted to investigate the relationship between quality of life and "irritating" stimuli like methacholine and dry air. Asthma is a chronic disorder of the airways resulting in variable symptoms and airflow limitation over time. The aim of study III was to evaluate the relationship between quality of life as assessed by AQLQ and these "objective" measures of asthma. In conformity with the finding in study I, we found no correlation between quality of life scores and the other parameters. In a similar cross-sectional study, 58 children with a wide range of asthma severity and treatment were examined [Wilson et al., 2001]. The aim was to correlate the results of recommended methods for assessment of inflammation with measurement of asthma control. Exhaled nitric oxide (NO), serum eosinophilic cationic protein (ECP), and induced sputum (processed for eosinophil count and ECP level) were related to recent symptoms, lung function, and bronchial responsiveness, but not to quality of life. The researchers found no significant correlation between the results of any method. There was no association of any inflammatory markers with current symptoms and only a weak relationship between inflammatory and physiological markers. They concluded that the place of these markers remains unclear, and their use in clinical practise needs further investigation by long-term longitudinal studies.

In an editorial letter, Hoekstra discusses if eosinophil-derived proteins could be used to diagnose or to monitor childhood asthma [Hoekstra].The number of eosinophils in peripheral blood, and the serum concentration of ECP and eosinophils-derived neurotoxin (EDN), as well as the urinary concentration of EDN are increased in asthmatic children, as compared to healthy controls. However, a clear overlap exists between children with asthma and healthy controls, indicating that differences between groups cannot easily be extrapolated to individuals. Another argument is that elevated levels of serum ECP are not specific for asthma. The conclusion was that there is increasing evidence that eosinophil-derived proteins cannot be used to diagnose or monitor asthma in children.

It has been argued that these poor correlations arise through imprecise measurement (both of clinical status and of quality of life). To determine whether the weakness of association is solely attributable to instrument noise, or whether quality of life is a distinct component in asthma health status, Juniper and colleagues conducted a factor analysis. With a data base from three clinical trials (n=763), factor analysis was used to explore the relationship between quality of life measured by AQLQ, and conventional measurement of clinical asthma status (symptoms, airway calibre, and rescue β_2 –agonist use). Analysis of 21 different outcomes revealed that, overall asthma health status has four components (factors) that can be named: "asthma specific quality of life", "airway calibre", "night-time clinical problems" and "day-time clinical problems". All 21 outcome measures fell into anyone of four distinct groups. The researchers conclude that, although some of the weakness in correlation between clinical outcomes and quality of life may be due to instrument "noise", the weakness is mainly due to quality of life being a distinct component of asthma health status. If the poor correlation was due to instrument "noise" there would have been no separations into such clinically sensible groups. It is emphasized that this does not imply that there are only four factors determining and categorising asthma. Other factors might be found among the large number of cellular and biochemical features of asthma (e.g., eosinophils in sputum or exhaled nitric oxide) not yet widely recognised in evaluating asthma status in clinical trials. These inflammatory markers may be associated with other factors as yet unidentified. The study authors conclude that patient well-being, quality of life, cannot be imputed from clinical outcome, and that it must be measured and interpreted independently [Juniper et al., 2004].

In our studies, where we have focused on patients with mild asthma, lacking relationships between quality of life and "objective" measurement may also be explained by the fact that most patients had high quality of life scores already at the first visit. In the intervenient study IV, the high scores at baseline did not leave much space for improvement**,** and consequently it is not likely that a significant correlation to the changes in "objective" measurements will be found. In study III, the inter-individual range in quality of life scores was limited which probably contributed to the lack of correlation between quality of life scores and the "objective" parameters.

Gender difference in Quality of Life

In study I women tended to have lower quality of life scores than men with regard to all domains and overall estimation. This difference was significant, however, only for the environment domain. This was also reflected by the assessment of symptoms using the VAS. In total, 60% of the patients in the study were women while 71% of the patients who experienced symptoms in groups C and D (VAS>20 mm) were women. Several studies have shown that women tend to experience greater impairment of quality of life than men with similar clinical asthma severity [Leidy et al.; Juniper et al.; 1992; Marks et al., 1992; Marks et al., 1993; Hyland].

A tendency towards higher symptom scores in asthmatic women compared to men with asthma was found when the AQLQ was constructed [Juniper et al., 1992]. The reason for the gender difference is not clear. It has been claimed that the difference cannot be explained by higher prevalence of asthma or rhinitis in women [Stenberg et al., 1993 a]. Women seem to be more annoyed by physical climate factors than men and seem to run the risk of "sick building syndrome" to a higher extent than men [Tamblyn et al.; Stenberg et al., 1993 a]. Some authors claim that this is the result of a tendency towards higher reporting among women, [Tamblyn et al.] whereas others disagree with that claim [Stenberg et al., 1993 b].

The effect of smoking on Quality of Life, exhaled NO and treatment with steroids

As our intention has been to study a population of patients with mild asthma in primary care centres, we did not exclude smokers or ex-smokers. In study I, 36% were smokers and 37% ex-smokers. We found that lung function was impaired in smokers (FEV_1 72.8 [1.4] % of predicted) compared to ex-smokers (FEV_1 80.2 [2.6] % of predicted value) and non-smokers (84.2 [1.9] % of predicted value). The finding of impaired lung function in smokers compared with non smokers and ex-smokers suggests that COPD induced by smoking may have been present in some of the patients.
In study II the "poor perceivers", patients who did not experience symptoms according to the VAS and had impaired lung function (group B)**,** had lower quality of life scores than patients in group A, at visit one. In this group, 55% were smokers compared to 4% of the patients with normal lung function (group A). It seems likely that smokers are more prone to deny airway symptoms, and there are findings supporting a higher prevalence of poor perceivers among smokers [Massasso et al., 1999 a; Massasso et al.,1999 b]. The patients in group B were also older than patients in group A. Reduced perception of bronchoconstriction has been reported in the elderly [Ekici et al.; Connolly et al.].
Our results in study II indicate that adjustment of therapy, especially in smokers and elderly asthmatics, could not only be based on experienced symptoms. The data strongly support the use of a regular measurement of lung function in the long term management of asthma. It is evident that lung function often is not measured in clinical practice [Rabe et al., 2004].

In a recently published study, it was found that smokers with mild asthma were less sensitive to the therapeutic effect of a low dose of inhaled beclomethasone (400 μg), administered for a 12 weeks period, than non-smoking asthmatics. There was an improvement in morning PEF in the non-smoking group but not in the smoking group. Smokers receiving low dose inhaled corticosteroids had more exacerbations than non-smokers. There were no differences between the outcome measurement of smoking and non-smoking groups at a higher dose of medication (2000μg per day) [Tomlinson et al.].
In another study it was shown that there was a significant improvement in FEV_1 and asthma control after oral prednisolone, compared to a placebo, in lifelong non-smokers with asthma but not in smokers with asthma. Ex-smokers with asthma had a significant improvement in morning and night PEF, but not in FEV_1 or asthma control score [Chaudhuri et al.].

The levels of exhaled NO are reduced in smokers compared to non-smokers [Kharitonov et al., 1995]. It has also been shown that exhaled NO levels are higher in smokers with asthma than in healthy smokers without asthma [Horvath et al.]. In study IV there were 12 smokers in the fluticasone group and 6 in a placebo group. The pre-treatment level on exhaled NO was similar in the two groups, 19.3 ppb in the fluticasone group and 20.7 ppb in the placebo group. It is possible that the difference in smoking habits between the groups contributed to the lack of difference in quality of life after three months of treatment.

Poor perception of asthma

In study II we identified patients with a poor perception of symptoms. All patients answered the question “Have you experienced any asthma problems or breathing difficulties during the last two weeks”. From this simple question, all patients indicated few symptoms on the VAS (0-20 mm). However, when answering the quality of life questionnaire (AQLQ) with 32 questions, patients with impaired lung function (group B) had significantly lower scores than patients with normal lung function (group A). Patients in group B may therefore be called “poor perceivers”. Adjusted treatment in group B resulted in a considerable improvement of quality of life, up to the same level as the patients with initially normal lung function. On an individual basis, a clinically relevant improvement of quality of life was observed in more than half of the patients (total score improvement >0.5) in the group with poor perceivers, compared to approximately 25% in the other group. Lung function also improved, but not up to the same level as in the other group (Figure 6.)
Our results indicate that adjustment of therapy cannot entirely be based on the patients having experienced symptoms, but should also include lung function measurements. This may be of particular importance in elderly and smoking asthmatic subjects, which also is important to emphasize considering the infrequent use of spirometry found in the AIRE-studies [Rabe et al., 2000; Rabe et al., 2004].

Effect of fluticasone on Quality of Life in steroid naive patients with mild asthma

In study IV we examined 70 patients with mild asthma, not treated with steroids, who were randomized for treatment with inhaled fluticasone (250μg b i d) or a placebo for three months. Quality of life scores were high already before treatment and increased slightly up to 6.0 in both groups after three months of treatment. The increase was below the minimal important difference (MID<0.5) in both groups. There were no significant differences between the two groups with regard to change in quality of life. As previously mentioned, all patients suffered from very mild asthma, according to the inclusion criteria, which did not leave much room for improvement.

Effect of fluticasone on markers of inflammation

In the fluticasone treated group, we found a significant decrease in bronchial responsiveness to methacholine, which was not different from a placebo. It has been shown that airway hyper-responsiveness (AHR) is reduced by treatment with inhaled corticosteroids (ICS). Ketchell and associates investigated the early effect of inhaled fluticasone on airway responsiveness in 38 non-smoking steroid-naive patients with mild atopic asthma (FEV_1>70% of predicted value). They demonstrated a reduction in AHR to adenosine 5'-monophosfate (AMP), but not to histamine, within 2 hours of a single inhalation of fluticasone [Ketchell et al.]. In another study, twelve subjects with mild asthma were treated with a placebo and three doses (50, 100, and 400μg twice daily) of mometasone furoate. All three doses demonstrated similar attenuation of allergen-induced airway hyperresponsiveness as compared to placebo [Inman et al.]. A single dose of inhaled budesonide (2400μg) resulted in a significant 2, 2-fold improvement in airway responsiveness to hypertonic saline [Gibson et al.], and treatment with 1000μg of fluticasone propionate twice daily for three months attenuated the bronchial methacholine response by a 2.8 doubling dose steps. Four weeks after cessation of therapy, there was still a significant improvement in airway responsiveness to methacholine [Booth et al.]. Lee and colleagues compared the effect of two different corticosteroids on airway responsiveness, in mild-to-moderate persistent asthma in 28 patients who received four weeks of treatment with either ciclesonide (CIC) or fluticasone propionate (FP). There was no significant difference between the two corticosteroids with regard to the effect on bronchial responsiveness, which was the primary outcome. Their pre-treatment quality of life overall score was 6.12 in the CIC treated group and 6.22 in the FP group, indicating very mild asthma [Lee et al.]. Unfortunately, their study was under-powered to evaluate secondary outcomes such as quality of life.

In children with mild asthma 12 weeks of treatment with fluticasone propionate (200μg twice daily) did not influence bronchial responsiveness to methacholine or the absolute values of FEV_1, compared to treatment with a placebo. However, symptom scores, frequency of the use of rescue medication, wheezing, and a global parent evaluation were improved [Arets et al.].

In study IV we showed that inhaled fluticasone significantly reduced bronchial responsiveness to dry air hyperventilation. This effect differed significantly when compared to placebo treatment. Already in 1991, Vathenen and colleagues showed an effect of inhaled budesonide on bronchial reactivity to eucapnic dry air hyperventilation in patients with asthma. They compared the effect of six weeks of treatment with budesonide (800 μg twice daily) on bronchial reactivity to histamine, exercise and eucapnic hyperventilation of dry air in 40 subjects with asthma. They found a similar magnitude of change in bronchial reactivity to all three stimuli [Vathenen et al.]. It has also been shown that treatment with inhaled steroids reduces the severity of exercise induced bronchoconstriction [Henriksen et al.; Waalkens et al.].

After three months of treatment there was a significant decrease in exhaled NO in the fluticasone group. The level of exhaled NO fell significantly only in those with high pre-treatment values, whereas neither fluticasone nor placebo treatment influenced the level of exhaled NO in those who had normal values (<20ppb) prior to treatment.
Several studies have shown that corticosteroids reduce exhaled NO in asthma [Aziz et al.; Lim et al.; van Rensen et al.; Kharitonov et al., 2002]. In a study performed on 126 children with mild-to-moderate persistent asthma, fluticasone and montelukast were compared. It was found that children who responded to fluticasone but not to montelukast had higher exhaled NO values, impaired pulmonary function and were more responsive to methacholine [Szefler et al.].

It has been proposed that, since elevated levels of NO have been reported in diseases other than asthma, the application of measurements of exhaled NO as a diagnostic tool may be best suited for tracking the degree of inflammation within individual patients rather than for discriminating one airway disease from another [Sanders].

It has been discussed whether or not exhaled NO could be of clinical value to diagnose asthma, to monitor response to treatment, compliance, disease activity and to predict acute exacerbation. An advantage is that measurement of exhaled NO is non-invasive, easy to perform both on adults and children, and convenient for the patient. A disadvantage however is, that levels of exhaled NO are influenced by smoking and atopy and that exhaled NO-level do not seem to be elevated in all asthmatic subjects, which has been demonstrated in the present thesis (study III).

Should patients with mild asthma be treated with inhaled steroids

It has been debated whether or not patients with mild asthma should be treated with inhaled corticosteroids. In study IV, treatment with steroids did not lead to clinically meaningful improvement in quality of life. On the other hand, treatment improved, and to some extent normalized a number of the surrogate markers of inflammation and disease activity. The important question concerns how early intervention may prevent progression toward fixed obstruction and a more severe disease. There are studies indicating that early treatment with steroids may have long-term beneficial effects on lung function and bronchial responsiveness [Haahtela et al., 1991; Selroos et al., 2004; Pauwels et al.]. It is not clear however, whether long-term outcomes of asthma treatment are more successful if treatment is based on supplementary information obtained by measurement of surrogate markers of inflammation in addition to symptoms.
In the 1990's Osterman and colleagues studied 75 adult patients, mostly with mild asthma, diagnosed during the previous year. The aim of the study was to investigate whether treatment with a low daily dose of 400μg inhaled budesonide influenced the progress of asthma. They concluded that early treatment with a low dose of budesonide improves airway function and decreases bronchial responsiveness, but the improvements are short-term if treatment is not continued. Quality of life was not used, however, as an outcome in that study. During a 6-month follow up period, without treatment with inhaled steroids, a slight deterioration of the disease occurred in most of the patients, and 10 out of 35 patients discontinued due to exacerbation [Osterman et al.].

Few studies address the question of how long inhaled steroids should be continued after remission, whether the dose can be reduced and what kind of a dosage regimen should be adopted [Haahtela, 1999]. It has been shown that considerably long periods of treatment with steroids do not fully reverse the inflammatory changes in the airways, even in patients with mild asthma [Laitinen et al.].

Atopic asthma symptoms often seem to disappear at puberty. However, subjects at this age may experience unexpected, often serious asthma attacks. In 52 steroid-naive adolescents, with mild-intermittent asthma, increased airway responsiveness to methacholine was demonstrated in most of the patients and found to be severe in 36.5% and moderate in 32.7%. In addition the concentration of exhaled NO was significantly higher in asthmatics, as compared with control subjects. The study authors suggest that early intervention with anti-inflammatory drugs may be indicated for a significant proportion of patients in this age group [Spallarossa et al.].

It is obvious that long-term treatment with inhaled steroids suppresses the disease by affecting the underlying airway inflammation. Symptoms often disappear, and lung function improves. Bronchial responsiveness continues to decrease for many months or even years after continuous treatment with steroids. In study IV, three months of treatment with inhaled steroids did not improve quality of life in a clinically meaningful way. To my knowledge there is no real long-term study addressing the effect of treatment with inhaled corticosteroids, on quality of life of asthmatic patients with mild disease.

Regular or intermittent treatment with steroids in mild asthma

In modern guidelines, there are recommendations for treatment of mild asthma which allow for stepping up and stepping down therapy. However, this approach is often not followed in general practice. In a British study of 17.206 adult asthma patients from 102 domestic practices a majority of patients were under-treated as compared to recommendations given in the guidelines. Between 55 and 69% of the patients at steps 1-3 should be treated at a higher step [Neville et al.].

In a recently published study by Boushey and colleagues, daily versus as-needed corticosteroid treatment for patients with mild persistent asthma was evaluated. Inclusion criteria were physician-diagnosed asthma, an age of 18 to 65 years, $FEV_1 > 70\%$ of predicted value and reversibility >12%, and at least 200 ml after inhalation of a bronchodilator. Patients who had taken corticosteroids during the previous six weeks were excluded. The patient population was similar to the population in study IV, but in contrast to our study smokers were excluded. They compared the level of asthma control obtained with the use of an intermittent treatment with corticosteroids, based on an action plan when asthma symptoms worsened, intermittent treatment plus daily treatment with a controller medication, either corticosteroid (budesonide) or a leukotrien-receptorantagonist (zafirlukast). The three treatments yielded similar increase in morning PEF, rates of exacerbations and increase in quality of life scores. Budesonide reduced sputum eosinophils, exhaled NO, bronchial reactivity, and increased the number of symptom-free days more than the other treatments. Quality of life was measured by the AQLQ(S) and the pre-treatment overall score was 5.9 in the intermittent treatment group and 5.8 in the other two groups. The quality of life scores increased in all three groups, and the changes were not significantly different between the groups. The authors concluded that the data supported the possibility to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsened [Boushey et al.].

Should asthma treatment be adjusted by the results of measures of inflammation

In our study we found a weak, but statistically significant, correlation between a decrease in exhaled NO levels and improved quality of life (overall score) in the fluticasone treated group. These findings indicate that the measurement of exhaled NO may be a useful tool in the guidance of treatment of patients with mild asthma. Otherwise, we found no correlation between changes in quality of life scores and changes in the other parameters.

A study by Laprise et al evaluated the association of asthmatic patients with asymptomatic AHR to clinical and immunohistological indicia. After 2 years patients with asymptomatic AHR had bronchial biopsies with more subepithelial fibrosis compared with control subjects [Laprise et al.].

In a two-year, prospective study, asthma treatment was guided either by symptoms and lung function alone in one group, or by the result of bronchial responsiveness to methacholine in

addition, in the other group. The addition of a bronchial methacholine challenge improved asthma control, but also almost doubly increased the dose of inhaled corticosteroids [Sont et al.].

In a recent study by Smith and colleagues adjustment of the dose of inhaled corticosteroids was managed on the basis either of exhaled NO measurements or based on conventional guidelines. They found that, with the use of exhaled NO measurements, a maintenance dose of inhaled corticosteroids may be significantly reduced without compromising asthma control. The final mean daily doses of fluticasone were 370µg per day in the "exhaled NO" group compared to 641µg per day in the control group [Smith et al.].

If a measurement of inflammation is to be used clinically, it must be inexpensive and quick to perform. It must also be able to be used on individual patients, not only to distinguish between groups. Furthermore it must provide information not available with current clinical tools [Wilson, 2002].

In clinical practice we deal with individual patients. It is difficult to extrapolate results from experimental studies of markers of inflammation to the clinical management of individual patients. Asthma is considered to be caused by inflammation. No current marker of inflammation is both highly sensitive and specific to diagnose asthma. It has also been discussed whether or not markers of eosinophil activation and exhaled NO reflect atopy and not asthma [Zimmerman et al., Remes et al., Carlsen et al.]. It seems likely that asthma is a clinically indefinable syndrome consisting of a number of overlapping dimensions, so that concentrating on only one aspect of the disease will not be fully relevant. It is evident that some patients have symptoms with no increase in inflammatory markers [Wilson et al., 2000 a;Wilson et al., 2000 b, Wilson et al., 2001;Turner et al.], while others are in remission of asthma, but still show evidence of increased markers of inflammation [van den Toorn et al.; Boulet et al.]. From these data and our studies, it is evident that current inflammation only partly reflects clinical asthma.

There are thus still a number of issues that remain to be solved:

How does inflammation of the airways translate into clinical symptoms of asthma?

Should patients who have increased markers of inflammation, but few asthmatic symptoms be treated with anti-inflammatory therapy?

Should patients with symptomatic asthma but no signs of airway inflammation be treated with anti-inflammatory drugs?

Should patients with evidence of airway inflammation, but without asthma symptoms, such as patients with hay fever, be treated to prevent future asthma?

These questions will not be answered by short-term studies. Long-term population studies that follow patients from childhood to adulthood are required. Valuable studies should focus on the relationship between markers of inflammation and short- and long-term outcome. The effect of early treatment with inhaled steroids and other anti-inflammatory therapies on long-term outcomes, can be sought [Wilson et al, 2000 b].

Conclusions

In asthma patients in primary care:

– The majority have high quality of life scores.

– Females, smokers, ex-smokers, non-atopics and elderly patients have low quality of life scores as compared to male, non-smoker, atopic and younger patients.

In steroid-free patients with mild asthma:

– We have found no correlation between quality of life and parameters such as lung function, reversibility to a bronchodilator, bronchial reversibility to a direct and an indirect stimuli, and exhaled NO.

– Approximately 75% had a positive methacholine challenge test, 50% had elevated exhaled NO values and approximately 30% were found positive on a dry air provocation test.

– There was significant co-variation between exhaled NO and bronchial responsiveness to methacholine and dry air.

–Treatment with fluticasone for three months induced a decrease in methacholine and dry air responsiveness and a reduction in exhaled NO, but had no effects on quality of life.

Poor perceivers:

– Patients with mild asthma and impaired lung function, who regard themselves as free of symptoms, experience a clinically relevant improvement in quality of life following adjustment of therapy.

Svensk sammanfattning

Quality of Life and markers of inflammation
A study of asthma in primary care

Syftet har varit att studera livskvaliteten hos patienter med lindrig astma för att se om det föreligger något samband mellan livskvalitet, lungfunktion, bronkiell reaktivitet och inflammationsmarkörer.

Bakgrund

Astma är en kronisk sjukdom som oftast diagnostiseras och behandlas i primärvården. Huvuddelen av patienterna har lindrig eller måttligt svår astma. Vid en kronisk sjukdom som astma, som man normalt inte kan bota och där patienten ofta står på livslång behandling är det viktigt att ta hänsyn till patientens upplevelse av sin sjukdom och hans livskvalitet.

På senare år har det blivit vanligt att inkludera frågeformulär om hälsorelaterad livskvalitet i klinisk forskning. Formulären är standardiserade och mäter olika aspekter på sjukdomen som symtom, aktivitetsbegränsningar, emotionella problem och besvär som är relaterade till exponering för omgivningsstimuli. Det vanligast förekommande formuläret är Asthma Quality of Life Questionnaire (AQLQ) konstruerat av Juniper och kollegor. Det har goda mätegenskaper och har visats kunna upptäcka små men viktiga förändringar över tiden.

Behandlingsrekommendationer för astmabehandling vid kroniska besvär baseras oftast på symtom och lungfunktion. Lungfunktionen har dock endast en begränsad samvariation med förändringar i livskvalitet. Astma anses nu vara orsakad av inflammation i luftrören. Att minska inflammationen har blivit det primära målet vid astmaterapi. Inom forskningen har det varit av stort intresse att mäta biologiska markörer med vilka den inflammatoriska processen skall kunna följas. Undersökningar av utandad kväveoxid (NO), bronkiell reaktivitet, reversibilitet av luftrörsvidgande medicin och lungfunktion har bedömts avspegla kliniskt status. För kliniker skulle det vara av stor vikt att ha tillgång till objektiva markörer vid diagnos och uppföljning av astma.

Vissa patienter, så kallade ”poor perceivers” upplever inte besvär trots att deras sjukdom och lungfunktion försämrats. Det är risk att denna grupp patienter inte blir adekvat behandlade och det är av intresse att undersöka om deras livskvalitet och lungfunktion förbättras om behandlingen ökas.

Det är viktigt att undersöka om patienter med mild astma har vant sig vid sina symtom och om det föreligger tecken på inflammation i luftrören. Värdet av tidig behandling av dessa patienter med kortison har varit mycket diskuterat och det är av stort intresse att undersöka om tidig behandling med kortison påverkar livskvalitet och inflammation i luftvägarna.
Trots att huvuddelen av patienterna har lindrig till måttligt svår astma, så har endast ett fåtal studier blivit utförda på denna patientkategori. Genom att kategorisera patienterna beroende på symtom och lungfunktion samt genom behandling med farmaka kommer kunskaperna om livskvaliteten hos dessa patienter med mild astma att öka.

Studier

Studie I

I studie I var avsikten att bedöma livskvaliteten hos astmapatienter i primärvården. 120 patienter med varierande svårighetsgrad av astma delades upp i fyra grupper beroende på lungfunktion och svar på en enkel symptomfråga, mätt med visuell analogskala, VAS. Grupp A (symtomfri, VAS≤20 mm, och normal FEV_1); B (symtomfri, VAS≤20 mm, låg FEV_1); C (VAS>20 mm, normal FEV_1) samt D (VAS>20 mm, låg FEV_1). Livskvalitet bedömdes med Asthma Quality of Life Questionnaire, AQLQ, och behandlingen registrerades. Livskvaliteten var signifikant olika i grupperna. Högst poäng med bäst livskvalitet, 6.0 i grupp A, 5.4 i grupp B, 4.8 i grupp C och 4.6 i grupp D. Det noterades låg korrelation mellan livskvalitet och FEV_1 men en relativt hög till VAS ($r=0.47$ till 0.67; $p<0.0001$ för alla domäner). Besvär av symtom (VAS>2) var tydligt relaterat till låga poäng på omgivningsdomänen. Kvinnor upplevde sämre livskvalitet än män på alla domäner och totalt. Patienter utan kortisonterapi hade bättre livskvalitet än de som tog kortison.
***Sammanfattning*:** Livskvaliteten bland patienter med astma i primärvården korrelerar bättre med svaret på en enkel symtomfråga än med lungfunktionen. Huvuddelen av patienterna har en god livskvalitet vilket talar för relativt ringa symtom och bara måttliga begränsningar av aktiviteter.

Studie II

I studie II önskade vi undersöka om patienter som upplever sig symtomfria men som har nedsatt lungfunktion, så kallade ”poor perceivers”, uppnår en förbättrad livskvalitet och lungfunktion om behandlingen ökas. Fyrtiotvå patienter som tidigare deltagit i studie I och som inte haft astmasymtom under de senaste två veckorna delades i två grupper: Grupp A med normal lungfunktion, (n=22), och grupp B med nedsatt lungfunktion (n=20), se studie I. Lungfunktion, symtom och livskvalitet mättes vid start och efter tre månader. Behandlingen ökades vid start i grupp B men inte i grupp A. Livskvaliteten var signifikant lägre i grupp B vid första besöket och förbättrades upp till samma nivå som i grupp A efter tre månaders utökad terapi. Lungfunktionen förbättrades signifikant endast i grupp B, men nådde inte upp i samma nivå som i grupp A.
***Sammanfattning*:** Utökad terapi förbättrar livskvaliteten även hos patienter som inte upplever symtom, så kallade ”poor perceivers”. Astmabehandling bör därför vägledas av både symtom och lungfunktion.

Studie III

I studie III var syftet att undersöka förhållandet mellan livskvalitet och inflammationsmarkörer: Lungfunktion, reversibilitet av luftrörsvidgande medicin, bronkiell reaktivitet på ett direkt och ett indirekt stimulus samt utandad kväveoxid (NO).
Sjuttiosju vuxna astmapatienter som upplever sig besvärsfria (VAS<30 mm), och som inte behandlades med kortison under de senaste tre månaderna medverkade. Lungfunktion, reversibilitet av luftrörsvidgande medicin, bronkiell reaktivitet för provokation med metakolin och torrluft, samt utandad NO, mättes. Atopi mättes med IgE antikroppar. Livskvaliteten mättes med Asthma Quality of Life Questionnaire, (AQLQ).

Vi fann ingen korrelation mellan livskvalitet och något av de övriga måtten. Patienter med förhöjd reversibilitet och stegrad reaktion på provokation med torrluft hade som grupp sämre livskvalitet i jämförelse med patienter med normala värden. Patienter med förhöjda värden på utandad NO hade bättre livskvalitet i jämförelse med patienter med normala värden. 59 av 77 patienter hade positiv metakolintest, 22 av 77 hade positiv torrluftsprovokation och 37 av 73 hade förhöjda värden på utandad NO.

Sammanfattning: Bland patienter med mild astma som ej tagit kortison fanns ingen korrelation mellan livskvalitet och parametrar på inflammation i luftrören. Det tycks som om ”objektiva” inflammationsmarkörer inte speglar patienternas livskvalitet och därför inte kan ge vägledning vid ställningstagande till val av terapi i denna grupp av patienter med mild astma.

Studie IV

I studie IV önskade vi undersöka om livskvalitet och inflammationsmarkörer påverkas av tre månaders behandling med kortison för patienter med mild astma.

Sjuttio patienter med mild astma som ej tagit kortison, se studie III, delades i två grupper och behandlades under tre månader med antingen fluticasone 250µg x 2 eller placebo. Livskvalitet och inflammatoriska markörer mättes före och efter behandlingen.

Behandling med fluticasone förbättrade inte livskvaliteten på ett kliniskt meningsfullt sätt. Man noterade en minskning av bronkiell reaktivitet mot metakolin och torrluft samt en sänkning av utandad NO i den kortisonbehandlade gruppen.

***Sammanfattning*:** Tre månaders behandling med fluticasone förbättrade inte livskvaliteten på ett kliniskt meningsfullt sätt hos patienter med mild astma. Däremot minskade reaktiviteten i luftrören för provokation med metakolin och torrluft, och graden av utandad kväveoxid minskade. Det är inte klart om detta utgör indikation till att behandla denna grupp av patienter med kortison.

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REFERENCES

Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994; 88:373-381

Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J 1993; 6:1368-1370

Anderson SD, Argyros GJ, Magnussen H, et al. Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. Br J Sports Med 2001; 35:344-347

Annett RD, Bender BG, Lapidus J, et al. Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? J Pediatr 2001; 139:854-861

Arets HG, Kamps AW, Brackel HJ, et al. Children with mild asthma: do they benefit from inhaled corticosteroids? Eur Respir J 2002; 20:1470-1475

Argyros GJ, Roach JM, Hurwitz KM, et al. Eucapnic voluntary hyperventilation as a bronchoprovocation technique: development of a standarized dosing schedule in asthmatics. Chest 1996; 109:1520-1524

Ashutosh K. Nitric oxide and asthma: a review. Curr Opin Pulm Med 2000; 6:21-25

ATS. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis **1991**; 144:1202-1218

ATS. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July **1999**. Am J Respir Crit Care Med 1999; 160:2104-2117

ATS. Guidelines for Methacholine and Exercise Challenge Testing-1999. Am J Respir Crit Care Med **2000**; 161:309-329

Aziz I, Wilson AM, Lipworth BJ. Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. Chest 2000; 118:1049-1058

Barr RG, Somers SC, Speizer FE, et al. Patient factors and medication guideline adherence among older women with asthma. Arch Intern Med 2002; 162:1761-1768

Bergner M, Bobbitt RA, Carter WB, et al. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19:787-805

Booth H, Richmond I, Ward C, et al. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. Am J Respir Crit Care Med 1995; 152:45-52

Boulet LP, Turcotte H, Brochu A. Persistence of airway obstruction and hyperresponsiveness in subjects with asthma remission. Chest 1994; 105:1024-1031

Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005; 352:1519-1528

Bousquet J, Knani J, Henry C, et al. Undertreatment in a nonselected population of adult patients with asthma. J Allergy Clin Immunol 1996; 98:514-521

Caress AL, Luker K, Beaver K, et al. Adherence to peak flow monitoring. Information provided by meters should be part of self management plan. Bmj 2002; 324:1157; author reply 1157

Carlsen KH, Halvorsen R, Pettersen M, et al. Inflammation markers and symptom activity in children with bronchial asthma. Influence of atopy and eczema. Pediatr Allergy Immunol 1997; 8:112-120

Chapman KR, Ernst P, Grenville A, et al. Control of asthma in Canada: failure to achieve guideline targets. Can Respir J **2001**; 8 Suppl A:35A-40A

Chapman KR. Impact of "mild" asthma omn health outcomes: findings of a systematic search of literature. Respiratory Medicine **2005**; 99:1350-1362

Chaudhuri R, Livingston E, McMahon AD, et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med 2003; 168:1308-1311

Cockcroft DW, Swystun VA. Asthma control versus asthma severity. J Allergy Clin Immunol 1996; 98:1016-1018

Connolly MJ, Crowley JJ, Charan NB, et al. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. Thorax 1992; 47:410-413

Cote J, Cartier A, Malo JL, et al. Compliance with peak expiratory flow monitoring in home management of asthma. Chest 1998; 113:968-972

Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 2000; 161:309-329

Dales RE, Spitzer WO, Schechter MT, et al. The influence of psychological status on respiratory symptom reporting. Am Rev Respir Dis 1989; 139:1459-1463

Diette GB, Wu AW, Skinner EA, et al. Treatment patterns among adult patients with asthma: factors associated with overuse of inhaled beta-agonists and underuse of inhaled corticosteroids. Arch Intern Med 1999; 159:2697-2704

Drazen J, Israel E. Treating mild asthma--when are inhaled steroids indicated? N Engl J Med 1994; 331:737-739

Ehrs PO, Nokela M, Ställberg, B. Hjemdahl, P. Wikström Jonsson, E. Brief questionnaires for patient reported outcomes in asthma-validation and usefulness in a primary care setting. Chest, in press

Ekici M, Apan A, Ekici A, et al. Perception of bronchoconstriction in elderly asthmatics. J Asthma 2001; 38:691-696

Erickson SR, Christian RD, Jr., Kirking DM, et al. Relationship between patient and disease characteristics, and health-related quality of life in adults with asthma. Respir Med 2002; 96:450-460

Ertle AR, Campbell EM, Hersh WR. Automated application of clinical practice guidelines for asthma management. Proc AMIA Annu Fall Symp 1996:552-556

Fuhlbrigge AL, Adams RJ, Guilbert TW, et al. The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines. Am J Respir Crit Care Med 2002; 166:1044-1049

Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. Am J Respir Crit Care Med 2001; 163:32-36

GINA. Global strategy for asthma management and prevention. NHLBI / WHO Workshop Report. Retrieved from http:www.ginasthma.com/ 2002, updated 2003

Goeman DP, Aroni RA, Stewart K, et al. Patients' views of the burden of asthma: a qualitative study. Med J Aust 2002; 177:295-299

Gustafsson LE, Leone AM, Persson MG, et al. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun 1991; 181:852-857

Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med **1991**; 325:388-392

Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med **1994**; 331:700-705

Haahtela T. Early treatment of asthma. Allergy **1999**; 54 Suppl 49:74-81

Hallstrand TS, Curtis JR, Aitken ML, et al. Quality of life in adolescents with mild asthma. Pediatr Pulmonol 2003; 36:536-543

Hedenström H, Malmberg P, Agarwal K. Reference values for lung function tests in females. Regression equations with smoking variables. Bull Eur Physiopathol Respir **1985**; 21:551-557

Hedenström H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: regression equations with smoking variables. Ups J Med Sci **1986**; 91:299-310

Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. Am Rev Respir Dis 1983; 128:993-997

Hoekstra MO. Can eosinophil-derived proteins be used to diagnose or to monitor childhood asthma? Clin Exp Allergy 1999; 29:873-874

Holzer K, Brukner P, Douglass J. Evidence-based management of exercise-induced asthma. Curr Sports Med Rep 2002; 1:86-92

Horvath I, Donnelly LE, Kiss A, et al. Exhaled nitric oxide and hydrogen peroxide concentrations in asthmatic smokers. Respiration 2004; 71:463-468

Hurwitz KM, Argyros GJ, Roach JM, et al. Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. Chest 1995; 108:1240-1245

Hyland ME. The Living with Asthma Questionnaire. Respir Med 1991; 85 Suppl B:13-16; discussion 33-17

Inman MD, Watson RM, Rerecich T, et al. Dose-dependent effects of inhaled mometasone furoate on airway function and inflammation after allergen inhalation challenge. Am J Respir Crit Care Med 2001; 164:569-574

Jacobs JE, van de Lisdonk EH, Smeele I, et al. Management of patients with asthma and COPD: monitoring quality of life and the relationship to subsequent GP interventions. Fam Pract 2001; 18:574-580

Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials 1989; 10:407-415

Janson C, Bjornsson E, Hetta J, et al. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med 1994; 149:930-934

Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med **1991**; 85 Suppl B:25-31; discussion 33-27

Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis **1992**; 145:1321-1327

Juniper EF, Guyatt GH, Epstein RS, et al. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax **1992**; 47:76-83.

Juniper EF, Guyatt GH, Ferrie PJ, et al. Measuring quality of life in asthma. Am Rev Respir Dis **1993**; 147:832-838.

Juniper EF, Guyatt GH, Willan A, et al. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol **1994**; 47:81-87

Juniper EF, Johnston PR, Borkhoff CM, et al. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. Am J Respir Crit Care Med **1995**; 151:66-70

Juniper EF. Assessing health-related quality of life in asthma. Can Respir J **1997**; 4:145-151

Juniper EF, Buist AS, Cox FM, et al. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest **1999 a**; 115:1265-1270

Juniper EF, Guyatt GH, Cox FM, et al. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J **1999 b**; 14:32-38

Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J **1999 c**; 14:902-907

Juniper EF, Buist AS. Health-related quality of life in moderate asthma: 400 microg hydrofluoroalkane beclomethasone dipropionate vs 800 microg chlorofluorocarbon beclomethasone dipropionate. The Study Group. Chest **1999 d**; 116:1297-1303

Juniper EF, Svensson K, O'Byrne PM, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. Eur Respir J **1999 e**; 14:1038-1043

Juniper EF. Using humanistic health outcomes data in asthma. Pharmacoeconomics **2001 a**; 19 Suppl 2:13-19

Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue beta2-agonist use? Respir Med **2001 b**; 95:319-323.

Juniper EF, Wisniewski ME, Cox FM, et al. Relationship between quality of life and clinical status in asthma: a factor analysis. Eur Respir J **2004**; 23:287-291

Kauppinen R RP, Sintonen H. Agreement between a generic and disease-specific quality-of-life instrument: the 15Dand SGRQ in asthmatic patients. Qual Life Res 2000; 9:997-1003

Ketchell RI, Jensen MW, Lumley P, et al. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5'-monophosphate in mild asthma. J Allergy Clin Immunol 2002; 110:603-606

Kharitonov SA, Robbins RA, Yates D, et al. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. Am J Respir Crit Care Med **1995**; 152:609-612

Kharitonov SA, Donnelly LE, Montuschi P, et al. Dose-dependent onset and cessation of action of inhaled budesonide on exhaled nitric oxide and symptoms in mild asthma. Thorax **2002**; 57:889-896

Koskela T, Hedman J, Ekroos H, et al. Equivalence of two steroid-containing inhalers: easyhaler multidose powder inhaler compared with conventional aerosol with large-volume spacer. Respiration 2000; 67:194-202

Laitinen LA, Laitinen A, Heino M, et al. Eosinophilic airway inflammation during exacerbation of asthma and its treatment with inhaled corticosteroid. Am Rev Respir Dis 1991; 143:423-427

Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998; 339:1194-1200

Laprise C, Laviolette M, Boutet M, et al. Asymptomatic airway hyperresponsiveness: relationships with airway inflammation and remodelling. Eur Respir J 1999; 14:63-73

Lee DK, Haggart K, Currie GP, et al. Effects of hydrofluoroalkane formulations of ciclesonide 400 microg once daily vs fluticasone 250 microg twice daily on

methacholine hyper-responsiveness in mild-to-moderate persistent asthma. Br J Clin Pharmacol 2004; 58:26-33

Legorreta AP, Christian-Herman J, O'Connor RD, et al. Compliance with national asthma management guidelines and specialty care: a health maintenance organization experience. Arch Intern Med 1998; 158:457-464

Leidy NK, Coughlin C. Psychometric performance of the Asthma Quality of Life Questionnaire in a US sample. Qual Life Res 1998; 7:127-134

Lim S, Jatakanon A, John M, et al. Effect of inhaled budesonide on lung function and airway inflammation. Assessment by various inflammatory markers in mild asthma. Am J Respir Crit Care Med 1999; 159:22-30

Lundbäck B, Nystrom L, Rosenhall L, et al. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. Eur Respir J **1991**; 4:257-266

Lundbäck B, Stjernberg N, Nystrom L, et al. An interview study to estimate prevalence of asthma and chronic bronchitis. The obstructive lung disease in northern Sweden study. Eur J Epidemiol **1993**; 9:123-133

Malmberg P, Larsson K, Thunberg S. Increased lung deposition and biological effect of methacholine by use of a drying device for bronchial provocation tests. Eur Respir J 1991; 4:890-898

Mancuso CA PM, Charlson ME. Effect of depressive symptoms on health-related quality of life in asthma patients. J GEN INTERN MED 2000; 15:301-310

Marks GB, Dunn SM, Woolcock AJ. A scale for the measurement of quality of life in adults with asthma. J Clin Epidemiol **1992**; 45:461-472

Marks GB, Dunn SM, Woolcock AJ. An evaluation of an asthma quality of life questionnaire as a measure of change in adults with asthma. J Clin Epidemiol **1993**; 46:1103-1111

Massasso DH, Salome CM, King GG, et al. Do subjects with asthma have greater perception of acute bronchoconstriction than smokers with airflow limitation? Respirology **1999 a**; 4:393-399

Massasso DH, Salome CM, King GG, et al. Perception of bronchodilation in subjects with asthma and smokers with airflow limitation. Respirology **1999 b**; 4:117-124

McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 1995; 4:293-307

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319-338

Morice AT, M. A randomiced trial of the initiation of asthma treatment. Asthma Gen Pract 1999; 7:7-9

Morris J, Perez D, McNoe B. The use of quality of life data in clinical practice. Qual Life Res 1998; 7:85-91

NAEPP. NAEPP Expert Panel report: guidelines for the diagnose and management of asthma-update on selected topics 2002.: (NIH publication no. 02-5075), 2002

Neville RG, Pearson MG, Richards N, et al. A cost analysis on the pattern of asthma prescribing in the UK. Eur Respir J 1999; 14:605-609

Nguyen BP, Wilson SR, German DF. Patients' perceptions compared with objective ratings of asthma severity. Ann Allergy Asthma Immunol 1996; 77:209-215

Osman LM, Calder C, Robertson R, et al. Symptoms, quality of life, and health service contact among young adults with mild asthma. Am J Respir Crit Care Med 2000; 161:498-503

Osterman K, Carlholm M, Ekelund J, et al. Effect of 1 year daily treatment with 400 microg budesonide (Pulmicort Turbuhaler) in newly diagnosed asthmatics. Eur Respir J 1997; 10:2210-2215

Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003; 361:1071-1076

Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. Eur J Respir Dis 1987; 70:171-179

Pellegrino R VG, Enright P, et al. Interpretative strategies for lung function testing. Eur Respir J 2005; In press

Poluzzi E, Resi D, Zuccheri P, et al. Use of anti-asthmatic drugs in Italy: analysis of prescriptions in general practice in the light of guidelines for asthma treatment. Eur J Clin Pharmacol 2002; 58:55-59

Postma DS, Kerstjens HA. Characteristics of airway hyperresponsiveness in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 158:S187-192

Quanjer PH, Lebowitz MD, Gregg I, et al. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. Eur Respir J Suppl 1997; 24:2S-8S

Rabe KF, Vermeire PA, Soriano JB, et al. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J **2000**; 16:802-807

Rabe KF, Adachi M, Lai CK, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol **2004**; 114:40-47

Redington AE, Howarth PH. Airway wall remodelling in asthma. Thorax 1997; 52:310-312

Remes S, Korppi M, Remes K, et al. Serum eosinophil cationic protein (ECP) and eosinophil protein X (EPX) in childhood asthma: the influence of atopy. Pediatr Pulmonol 1998; 25:167-174

Rowe BH, Oxman AD. Performance of an asthma quality of life questionnaire in an outpatient setting. Am Rev Respir Dis 1993; 148:675-681

Rutten-van Molken MP, Custers F, van Doorslaer EK, et al. Comparison of performance of four instruments in evaluating the effects of salmeterol on asthma quality of life. Eur Respir J 1995; 8:888-898.

Rönmark E. Asthma-Incidence,Remission and Risk Factors. Umeå University Medical Dissertations 1999; New series INo 630 SSN 0346-6612-ISBN 91-7191-708-X

Sanders SP. Nitric oxide in asthma. Pathogenic, therapeutic, or diagnostic? Am J Respir Cell Mol Biol 1999; 21:147-149

Sanjuas C, Alonso J, Prieto L, et al. Health-related quality of life in asthma: a comparison between the St George's Respiratory Questionnaire and the Asthma Quality of Life Questionnaire. Qual Life Res 2002; 11:729-738

Schipper H, Clinch J, Powell V. Definition and conceptual issues. 1996; Quality of life assessments in clinical trials. In: Spilker B, editor. Lippincot-Raven, Philadelphia:11-24

Schunemann HJ, Griffith L, Jaeschke R, et al. Evaluation of the minimal important difference for the feeling thermometer and the St. George's Respiratory Questionnaire in patients with chronic airflow obstruction. J Clin Epidemiol 2003; 56:1170-1176

Selroos O, Pietinalho A, Lofroos AB, et al. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest **1995**; 108:1228-1234

Selroos O, Lofroos AB, Pietinalho A, et al. Asthma control and steroid doses 5 years after early or delayed introduction of inhaled corticosteroids in asthma: a real-life study. Respir Med **2004**; 98:254-262

Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005; 352:2163-2173

Solway J. What makes the airways contract abnormally? Is it inflammation? Am J Respir Crit Care Med 2000; 161:S164-167

Sont JK, Willems LN, Bel EH, et al. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med 1999; 159:1043-1051

Spallarossa D, Battistini E, Silvestri M, et al. Steroid-naive adolescents with mild intermittent allergic asthma have airway hyperresponsiveness and elevated exhaled nitric oxide levels. J Asthma 2003; 40:301-310

Stenberg BHM, K. Sandström, M. Sundell, J. Wall, S. A prevalence study of sick building syndrome (SBS) and facial skin symptoms in office workers. Indoor air **1993 a**; 3: 71-81

Stenberg BW, S. Why do females report "sick buildin symptoms" more often than men? Indoor air **1993 b**; 1:399-404

Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:53-83

Strube G, Rudolf M. For and against. Should steroids be the first line treatment for asthma? Bmj 2000; 320:47-49

Ställberg B, Nystrom Kronander U, Olsson P, et al. Living with asthma in Sweden--the ALMA study. Respir Med 2003; 97:835-843

Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. J Allergy Clin Immunol 2005; 115:233-242

Tamblyn RM, RI M. Big sufferes of work related symptoms in office buildings-who are they? ATLANTA IAQ92, Environ for people.ASHRAE 1993:427-435

Taylor DM, Auble TE, Calhoun WJ, et al. Current outpatient management of asthma shows poor compliance with International Consensus Guidelines. Chest 1999; 116:1638-1645

Tinkelman DG, McClure DL, Lehr TL, et al. Relationships between self-reported asthma utilization and patient characteristics. J Asthma 2002; 39:729-736

Tirimanna PR, van Schayck CP, den Otter JJ, et al. Prevalence of asthma and COPD in general practice in 1992: has it changed since 1977? Br J Gen Pract 1996; 46:277-281

Tomlinson JE, McMahon AD, Chaudhuri R, et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax 2005; 60:282-287

Turner MO, Hussack P, Sears MR, et al. Exacerbations of asthma without sputum eosinophilia. Thorax 1995; 50:1057-1061

Waalkens HJ, van Essen-Zandvliet EE, Gerritsen J, et al. The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children. Dutch CNSLD Study Group. Eur Respir J 1993; 6:652-656

Walter SD. Number needed to treat (NNT): estimation of a measure of clinical benefit. Stat Med 2001; 20:3947-3962

van Den Toorn LM, Prins JB, Overbeek SE, et al. Adolescents in clinical remission of atopic asthma have elevated exhaled nitric oxide levels and bronchial hyperresponsiveness. Am J Respir Crit Care Med 2000; 162:953-957

van Rensen EL, Straathof KC, Veselic-Charvat MA, et al. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. Thorax 1999; 54:403-408

van Schayck CP, Dompeling E, van Herwaarden CL, et al. Continuous and on demand use of bronchodilators in patients with non-steroid dependent asthma and chronic bronchitis: four-year follow-up randomized controlled study. Br J Gen Pract 1995; 45:239-244

Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care **1992**; 30:473-483

Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care **1996**; 34:220-233

Ware JE, Jr. SF-36 health survey update. Spine **2000**; 25:3130-3139

Vathenen AS, Knox AJ, Wisniewski A, et al. Effect of inhaled budesonide on bronchial reactivity to histamine, exercise, and eucapnic dry air hyperventilation in patients with asthma. Thorax 1991; 46:811-816

Verleden GM, De Vuyst P. Assessment of asthma severity and treatment by GPs in Belgium: an Asthma Drug Utilization Research Study (ADUR). Respir Med 2002; 96:170-177

Vermetten FA, Boermans AJ, Luiten WD, et al. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. J Asthma 1999; 36:97-106

Verschelden P, Cartier A, L'Archeveque J, et al. Compliance with and accuracy of daily self-assessment of peak expiratory flows (PEF) in asthmatic subjects over a three month period. Eur Respir J 1996; 9:880-885

Williams JW, Williams K. Asthma-specific quality of life questionnaires in children:are they useful and feasible in routine clinical practice? Pediatr Pulmonol. 2003; 36:552-553

Wilson N, Pedersen S. Inflammatory markers in clinical practice. Am J Respir Crit Care Med **2000 a**; 162:S48-51

Wilson NM, Bridge P, Spanevello A, et al. Induced sputum in children: feasibility, repeatability, and relation of findings to asthma severity. Thorax **2000 b**; 55:768-774

Wilson NM, James A, Uasuf C, et al. Asthma severity and inflammation markers in children. Pediatr Allergy Immunol **2001**; 12:125-132

Wilson N. Measurement of airway inflammation in asthma. Curr Opin Pulm Med **2002**; 8:25-32

Viramontes JL, O'Brien B. Relationship between symptoms and health-related quality of life in chronic lung disease. J Gen Intern Med 1994; 9:46-48

Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). J Allergy Clin Immunol 1999; 103:376-387

Zimmerman B, Enander I, Zimmerman R, et al. Asthma in children less than 5 years of age: eosinophils and serum levels of the eosinophil proteins ECP and EPX in relation to atopy and symptoms. Clin Exp Allergy 1994; 24:149-155