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## Health-Related Quality of Life in COPD and Asthma - Discriminative and evaluative aspects

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Health-Related Quality of Life  
in COPD and Asthma  
*Discriminative and evaluative aspects*

*Elisabeth Ståhl*

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Abstract Ståhl E. Health-Related Quality of Life in COPD and Asthma - Discriminative and evaluative aspects. Department of Respiratory Medicine & Allergology, University Hospital, SE-221 85 LUND, Sweden  Background - The effects of intervention can be evaluated in different ways, and objective measurements of changes in lung function are commonly used as the outcome measure. Patient-reported outcome (PRO) is an umbrella term used for all patient-based assessments. One important PRO is health-related quality of life (HRQL), which may be used as an evaluative or discriminative measure. Objectives - To examine COPD subjects' completion of self-administered questionnaires. To study the evaluative effects with HRQL assessments after pulmonary interventions in COPD and asthma. Finally, to explore the discriminative possibility of using HRQL with regard to its relationship to other clinical indices and to disease severity in both COPD and asthma. Results - Most COPD subjects find it easy to complete questionnaires; however, the correlation of age with difficulty in completing questionnaires needs to be considered. Furthermore, it was shown that assessments of HRQL may be useful for evaluative purposes in COPD and asthma, although in COPD longer studies will be needed. The discriminative possibility of using HRQL data in COPD and asthma was shown. Symptoms correlated with HRQL, whereas between lung function and HRQL the relationship was weaker. HRQL seems to deteriorate with disease severity in COPD and asthma, as measured by lung function, or with age. However, great individual variation was noticed. Conclusions - The completion of up to five PRO questionnaires was well accepted by subjects with COPD. HRQL questionnaires might be used for evaluative purposes. HRQL questionnaires appear to have a possibility to be used for discriminative purposes in COPD and asthma, and for comparison of these diseases; however, this needs to be further explored. In homogeneous populations, used in evaluative studies, assessment of HRQL is valuable. In heterogeneous populations, a great variation in HRQL is likely to be seen and therefore there may be a chance to show a relationship between HRQL and lung function measures. However, within severity stages there is a great individual variation.			
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## ABBREVIATIONS

AcuteAQLQ	Acute Asthma Quality of Life Questionnaire
ANOVA	Analysis of variance
AQLQ	Asthma Quality of Life Questionnaire
AQLQ(S)	Asthma Quality of Life Questionnaire, Standardised version
ATS	American Thoracic Society
BODE	The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic Respiratory Questionnaire
EQ-5D	EuroQol 5D
ERS	European Respiratory Society
FACET	Formoterol and Corticosteroids Establishing Therapy
FDA	The US Food and Drugs Administration
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQL	Health-related quality of life
HS-COPD	Feeling Thermometer - Health States in COPD
IQOLA	International Quality of Life Assessment
ISAAC	The International Study of Asthma and Allergies in Childhood
ISH	Inventory of Subjective Health
ISOLDE	Inhaled Steroids in Obstructive Lung Disease in Europe



LWAQ	Living With Asthma Questionnaire
MCS	Mental Component Summary (SF-36)
MID	Minimal important difference
MiniAQLQ	Mini-Asthma Quality of Life Questionnaire
NHP	Nottingham Health Profile
NNT	Number needed to treat
NOT	Nocturnal Oxygen Therapy study
PCS	Physical Component Summary (SF-36)
PEF	Peak expiratory flow
PGWB	Psychological General Well-being Scale
PRO	Patient-reported outcome
SF-36	Medical Outcomes Study (MOS) Short Form 36
SF-6D	Short Form 6D
SGRQ	St George's Respiratory Questionnaire
SIP	Sickness Impact Profile
SWT	Shuttle Walking Test
TTO	Time Trade-Off
WHO	World Health Organization
WPAI-COPD	Working Productivity and Activity Index for COPD

## PAPERS

*The thesis is based on the following papers,  
referred to in the text by their Roman numerals.*

- I.** Ståhl E, Jansson S-A, Jonsson A-C, Svensson K, Lundbäck B, Andersson F. Health-related quality of life, utility, and productivity outcomes instruments: ease of completion by subjects with COPD.  
*Health and Quality of Life Outcomes* 2003; 1:18-25.
- II.** Ståhl E, Wadbo M, Bengtsson T, Ström K, Löfdahl C-G. Health-related quality of life, symptoms, exercise capacity and lung function during treatment for moderate to severe COPD.  
*J Outcomes Research* 2001; 5:11-24.
- III.** Ståhl E, Postma DS, Svensson K, Tattersfield AE, Eivindson A, Schreurs A, Löfdahl C-G. Formoterol used as needed improves health-related quality of life in asthmatic patients uncontrolled with inhaled corticosteroids.  
*Respiratory Medicine* 2003; 97:1061-1066.
- IV.** Ståhl E, Lindberg A, Jansson S-A, Rönmark E, Svensson K, Andersson F, Löfdahl C-G, Lundbäck B. Health-related quality of life is related to COPD disease severity.  
Submitted.
- V.** Szende A, Svensson K, Ståhl E, Mészáros A, Berta GY. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level.  
*Pharmacoeconomics* 2004; 22(8): 537-547.



# Health-Related Quality of Life in COPD and Asthma – *Discriminative and evaluative aspects*

by Elisabeth Ståhl

## INTRODUCTION

Survival and physiological measures alone do not represent the full experience of subjects with respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Reducing the personal and social burden of disease by improving subjects' symptoms, functional status and health-related quality of life (HRQL) also represents important goals.

### **COPD**

The concept of COPD is relatively 'new'. The terms earlier used were 'chronic bronchitis' and 'emphysema'. For many years various definitions of COPD have been used. During the 1970s, Fletcher and Peto defined COPD as a heterogeneous group of disorders, consisting of chronic bronchitis, emphysema and small airways disease, which lead to progressive, irreversible airflow obstruction [1]. Current definition according to the Global Initiative for Chronic Obstructive Lung Disease group (GOLD) guidelines is as follows: "COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." [2]. COPD is characterised by cough, sputum production and breathlessness associated with airflow obstruction. Smoking and occupational exposure to irritants such as dust and fumes are the major causes of COPD, approximately 85 to 90% of all cases being attributed to smoking. COPD is currently the fourth leading cause of death in the US and its prevalence is

increasing [3]. GOLD and the British Thoracic Society (BTS) as well as the European Respiratory Society (ERS) recommend a staging system for the assessment of COPD severity on the basis of FEV<sub>1</sub> % predicted normal value [2, 4, 5]. COPD affects middle-aged to elderly men, and with an increasing incidence, women with a history of smoking [6]. Respiratory diseases are among the three principal causes of lost working days worldwide, and COPD is responsible for the majority of the loss [7].

A considerable number of subjects have not been diagnosed as having COPD, although they may have the disease. Greater public awareness of COPD is therefore one of the main aims of GOLD. The incidence of respiratory symptoms and smoking may indicate that its prevalence will increase in the future. However, accurate estimates of prevalence, incidence and mortality are lacking for many countries. Published data from the south of Sweden shows a self-reported prevalence of 5.5% for chronic bronchitis and/or emphysema [8]. A somewhat higher value, about 7%, based on spirometry measurements has been reported in the north of Sweden [9], [10]. Recent published data estimate the prevalence of COPD in persons aged above 45 to be 8% according to the BTS criteria and 14% according to GOLD criteria [11].

Estimated prevalence in the US increased significantly during a 20-year period from 8.9 to 9.9% for men and from 0.9 to 4.2% for women [3]. The figure in Spain is similar: 9.1% [12]. International variations have been reported and vary from 3.2% in India to 22.9% in the inner-city population of Manchester, UK [13,14]. In a recent review of COPD prevalence studies, the overall prevalence in adults appears to lie between 4% and 10% [15]. Some of the variation can be attributed to methods of measuring COPD and its definition. The variation in methods of collecting data may be a reason for these discrepancies and the difficulty in differentiating between COPD and asthma. Moreover, subjects may have both diseases and only one diagnosis.

## **Asthma**

The Global Initiative for Asthma (GINA) guidelines give the following definition of asthma: “Asthma is a chronically inflammatory disorder of the airways. Chronically inflamed airways are hyperresponsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased inflammation) when airways are exposed to various stimuli, or triggers” [16]. Asthma triggers include viral infections, allergens, exercise and chemical products. Asthma is a disease that varies in severity in the individual subject, although airway inflammation could be chronically present. It cannot be cured by pharmacological means but can be treated and controlled by the use of preventive medication. Given adequate treatment, most subjects will live a normal life, both physically and socially.

Large epidemiological studies with a focus on asthma have been performed in several countries in Europe. In Sweden, the prevalence of subjects affected by asthma has been estimated to be 5 to 8%, i.e. about half a million individuals [17]. Swedish prevalence/incidence rate of asthma has been studied in the northern part of the country. The prevalence of asthma in adults in an industrial community increased from 3.1% in 1974 to 3.6% in 1981 [18]. In a survey performed in the mid-1980s in the same part of Sweden, the prevalence of asthma was almost 7% [9]. In another survey performed ten years later, the same population was contacted and the cumulative incidence for the ten-year period (1986-1996) was 3.2% among men and 4.5% among women [19]. After correction for symptoms common in asthma at the beginning of the observation period, the cumulative incidence rate was 1.7/1000 persons/year for men and 2.9/1000 persons/year for women. The increasing prevalence rate among adults during the last ten to twenty years may be explained by improved diagnosis of the disease. In southern Sweden the prevalence of physician-diagnosed asthma was about 8% in 2000 (Nihlén, U – personal communication).

In the US, asthma affects approximately 15 million persons, which means 6 to 7% of the population, and its prevalence was about the same in the rest of the westernised world [20-22]. In the UK the prevalence increased from 4% in 1973 to 9% in 1988 [23]. These prevalence rates may show some inconsistency because of varying definitions of asthma. In a recent study, using the questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence for current asthma is reported to be 12.6% and for ever-diagnosed asthma 16.4% among children aged between 7 and 12 years in the US [24].

In the present series of studies, the use of health-related quality of life (HRQL) instruments in subjects with COPD or asthma has been examined. The burden (feasibility) of completing a number of instruments was explored in subjects with COPD. Furthermore, the possibility to use HRQL instrument for evaluative and discriminative purposes after pulmonary interventions in COPD and asthma was tested. The relationship with other clinical measures was also studied. In addition, the possibility of using HRQL assessments as discriminator in relation to disease severity in COPD and asthma was examined.

## BACKGROUND

### **Health-related quality of life – definition of the concept**

Patient-reported outcome (PRO) is an umbrella term used for all patient-based assessments. PROs are by definition subjective and multidimensional. Examples of PROs are outcomes such as HRQL, symptoms, patient satisfaction, well-being and functional status. This thesis will focus on HRQL as the subjective outcome in COPD and asthma.

Various definitions of HRQL exist. The World Health Organization (WHO) definition of health is “not merely the absence of disease, but complete physical, psychological, and social well-being” [25]. HRQL refers to the physical, psychological and social domains of health that are unique to each individual [26]. It has been defined as follows: “HRQL is defined as the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy” [27]. Another definition is “HRQL can be defined as the functional effect of an illness and its consequent therapy upon a patient, as perceived by a patient” [28]. All definitions of HRQL are based on the subject's opinion.

Many factors such as age and socioeconomic and social support will affect many subjects' HRQL. It is generally agreed that improving the health of subjects is an important goal of a therapeutic intervention for both COPD and asthma [29]. It is also widely accepted that medical interventions should aim to improve not only objective clinical outcomes, but also patient-reported outcomes such as HRQL [30]. The burden of disease has been confirmed in both COPD and asthma. There are several studies showing that there is a significant deterioration of HRQL in subjects with COPD [31, 32]. A cross-sectional study of 321 COPD patients reported that those with a low FEV<sub>1</sub> predicted normal value have a substantial impairment in HRQL [32]. Asthma has been recognised as a major health problem, and despite the



availability of effective treatment, many subjects still suffer from symptoms and limitations in their everyday life [33].

### **Health-related quality of life – instruments for measurement**

A number of instruments have been developed to assess HRQL. These can be classified into two main types: generic and disease-specific/situation-specific.

There are generally accepted scientific methods for the development of an instrument for evaluating HRQL [34]. The construction of a generic instrument is usually based on large population surveys. The available generic instruments are all widely used and their measurement properties have been established.

The development of a new disease-specific instrument is advised by regulatory authorities to follow the following steps recommended by Juniper et al. [34]. Table 1 shows the steps involved.

**Table 1.** Steps involved in instrument development

<b>A.</b>	<b>Development</b>
1.	Specifying measurement goals
2.	Item generation
3.	Item reduction
4.	Questionnaire formatting
<b>B.</b>	<b>Testing</b>
1.	Pre-testing
2.	Reliability
3.	Responsiveness
4.	Validity
5.	Interpretability

All the development steps should be followed in order to obtain an evaluation of the measurement properties of the new instrument. For the developer and users of an HRQL questionnaire, the accumulation of reliability, responsiveness, validity and interpretability is an ongoing process.

### ***Generic questionnaires***

Generic HRQL questionnaires are designed to measure impaired HRQL in a general population as well as in subjects with various diseases, irrespective of the cause. A number of these instruments have been used in COPD and asthma.

Table 2 contains a list of examples of generic questionnaires.

**Table 2.** Examples of generic HRQL questionnaires

<b>Questionnaire</b>	<b>No. of items</b>	<b>Domains</b>
Sickness Impact Profile (SIP)	136	12 categories
Nottingham Health Profile (NHP)	45	6
Short Form 36 (SF-36)	36	8

#### *Sickness Impact Profile*

The Sickness Impact Profile (SIP) was developed by Bergner and colleagues in the 1970s and since then has been used extensively in clinical research [35]. It contains 136 items divided into a total of 12 categories. Three categories form a physical domain, four categories form a psychosocial domain and the remaining five categories are independent. The instrument describes activities associated with everyday living. The SIP was one of the first measures of overall health available to researchers. While it does appear to be a valid measure in COPD [36], in other studies improvements in inspiratory muscle strength were not associated with benefits in health using the SIP [37]. In addition, in the Nocturnal Oxygen Therapy (NOT) study of home oxygen treatment in respiratory insufficiency, there was no

significant effect on HRQL [38]. The SIP was included in an asthma study by Rutten-Van Mólken et al. and was not very responsive [39].

#### *Nottingham Health Profile*

Another commonly used generic questionnaire is the Nottingham Health Profile (NHP), also developed in the 1970s [40]. The NHP is easy to use and score and is available in a large number of translations. Its drawback, as with all generic questionnaires, is its lack of sensitivity to interventions. Two generic HRQL questionnaires, the Inventory of Subjective Health (ISH) and the NHP, were used in a study investigating the influence of inhaled corticosteroids on lung function and HRQL in patients with asthma and COPD [41]. Despite improvements in lung function, no improvements in HRQL were noticed.

#### *Short Form 36*

The most widely used generic questionnaire, the Medical Outcomes Study Short Form 36 (SF-36), has been a widely accepted generic HRQL measurement in recent years. The SF-36 includes 36 items divided into eight domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH). These domains create a profile of the subject. Two summary scores can also be aggregated: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The SF-36 has been normed for the general US population and for representative samples from Sweden, Denmark, Germany and the UK using translations and protocols developed in the International Quality of Life Assessment (IQOLA) Project [42-44]. It has been shown to be responsive in both COPD and asthma, though not to the same extent as disease-specific questionnaires [45]. SF-36 scores have been shown to be correlated with dyspnoea in COPD [46]. Another study in COPD showed changes in SF-36 scores related to changes of FEV<sub>1</sub> over time [47].

To summarize, the advantage of using generic questionnaires is that they allow comparisons of the burden of disease for various conditions. Descriptive information on the differences between patients and a healthy population can be obtained. However, the low sensitivity to change (responsiveness), spontaneous or due to intervention, found when using generic questionnaires can be seen as a drawback.

The development of specific HRQL questionnaires was prompted, among other things, by the low responsiveness of the generic HRQL questionnaires. Disease-specific questionnaires focus on the problems identified as being specifically important to subjects with a certain disease or condition.

### ***Disease-specific questionnaires***

In the past decade disease-specific HRQL instruments specifically aimed at COPD and asthma have been developed.

Table 3 shows examples of instruments specifically developed for respiratory diseases.

**Table 3.** Examples of disease-specific questionnaires for respiratory diseases

<b>Questionnaire</b>	<b>No. of items</b>	<b>Domains</b>
Chronic Respiratory Questionnaire (CRQ)	20	4
St George's Respiratory Questionnaire (SGRQ)	76	3
Asthma Quality of Life Questionnaire (AQLQ)	32	4
AQLQ(S), Standardised version	32	4
MiniAQLQ	15	4
Living With Asthma Questionnaire (LWAQ)	68	11
Asthma Quality of Life Questionnaire (AQLQ, [48])	20	4

### *COPD-specific questionnaires*

The first questionnaire developed for COPD was the Chronic Respiratory Questionnaire (CRQ) [49]. This questionnaire consists of 20 items in four domains: Dyspnoea, Fatigue, Emotion and Mastery. The patients respond to each item on a seven-point Likert scale. The questionnaire has been shown to be reliable and sensitive to change [50]. The CRQ was originally developed as an interviewer-administered questionnaire; however, a self-administered version has recently been developed and a validation study has been performed [51, 52]. The Minimal important difference (MID), which is defined as the smallest change shown to be of clinical relevance for the subject, is considered to be 0.5 on the seven-point CRQ scale [53, 54].

The best known and most frequently used disease-specific HRQL questionnaire for respiratory diseases, both for COPD and for asthma, is the St George's Respiratory Questionnaire (SGRQ) [29, 31, 55]. The SGRQ is a standardised, self-administered questionnaire for measuring impaired health and perceived HRQL in airways disease (COPD and asthma). It consists of 50 (76 weighted) items divided into three domains: Symptoms, Activity and Impacts. A score is calculated for each domain and a total score, including all items, is also calculated. Each item has an empirically derived weight. Low scores indicate a better HRQL. Recent publications by Paul W Jones confirmed suggestions that the MID is 4 on a scale of 0-100 [56-58].

### *Asthma-specific questionnaire*

The Asthma Quality of Life Questionnaire (AQLQ), developed by Elizabeth F Juniper, is one of the most commonly used standardised questionnaires for assessing HRQL in asthma [59].

The AQLQ evaluates 32 items in four domains of health-related quality of life that are of importance to subjects with asthma: activity limitation (11 items), symptoms (12 items), emotional function (5 items) and exposure to environmental stimuli (4 items). The subjects have to choose five activities (5 items out of 11 in the activity domain) that they are bothered by or have problems with. A list of suggested activities is provided to help the subjects to choose. Subjects are asked to recall their experiences during the previous two weeks and respond to each item on a seven-point Likert scale. The overall AQLQ score is calculated as the mean for all 32 items. Each domain score is calculated as the mean of the items included in the domain. A change of at least 0.5 on the seven-point AQLQ scale represents the MID [54, 60, 61].

The AQLQ(S) is the standardised version of the AQLQ, where the possibility to choose activities important for the subjects has been replaced by five generic items: strenuous exercise, moderate exercise, work-related activities, social activities and sleep [62].

The MiniAQLQ is a short version (15 items) of the AQLQ [63]. Elizabeth F Juniper has recently developed another HRQL questionnaire, the AcuteAQLQ, to be used in an emergency setting [64].

In all these questionnaires developed by EF Juniper, a high score means a better HRQL. The AQLQ, the AQLQ(S) and the MiniAQLQ are all available in an interviewer-administered format as well as in a self-administered format. The AcuteAQLQ is available in an interviewer-administered format.

Other specific HRQL questionnaires for asthma are the Living with Asthma Questionnaire (LWAQ), developed by Michael E Hyland [65], and the Asthma Quality of Life Questionnaire (AQLQ), by Marks [48, 66]. The LWAQ is a 68-item questionnaire divided into 11 domains: Social/Leisure, Sport, Holidays, Sleep, Work, Colds, Morbidity, Effects on others, Medication use, Sex, and Dysphoric

states and attitudes. Responses are given on a three-point scale. The AQLQ (Marks) is a self-administered questionnaire containing 20 items in four domains: Breathlessness and physical restrictions, Mood disturbance, Social disruption and Concerns for health. The responses to each item are given on a five-point scale.

Another HRQL questionnaire also used in asthma is the St George's Respiratory Questionnaire (SGRQ) [31, 55]. The SGRQ was developed for respiratory diseases such as COPD and asthma, but is mainly used in COPD and is therefore presented in that section.

### ***Preference-based questionnaires***

#### *EuroQol 5D*

The EuroQol 5D (EQ-5D) is a generic, preference-based utility questionnaire and consists of two parts, the EQ-5D VAS and the EQ-5D index [67]. The EQ-5D VAS is a visual analogue scale ranging from 0=death/worst possible health to 100=best possible health. The EQ-5D index is a five-item questionnaire. The items consist of mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each item has three levels: no problem, some problem and severe problem [67]. For the EQ-5D index, 0.03 has been regarded as the MID [68].

#### *Short Form 6D*

The Short Form 6D (SF-6D) is a health-state classification system constructed post hoc from 11 selected items from the SF-36 generic HRQL questionnaire [69]. The SF-6D is composed of six HRQL domains: physical functioning, role limitations, social functioning, pain, mental health and vitality, and is based on 11 selected items from the SF-36 instrument. The number of response options varies between four and six, depending on domain. In practice, subjects fill in the SF-36 questionnaire and their responses are then used to determine SF-6D scores.

### *Time Trade-Off*

The Time Trade-Off (TTO) includes a direct question offering a choice between twenty years in current health or shorter length of life in perfect health [70].

### *Health Utilities Index (HUI)*

The current version of the HUI3 has evolved from HUI1 and HUI2 [71, 72].

### *Feeling Thermometer with Health Marker States for COPD (HS-COPD)*

A future instrument for preference-based utilities may be the Feeling Thermometer using pre-defined Health Marker States or Clinical Marker States. The HS-COPD is being developed using Health Marker States relevant for COPD, and the instrument to complete is a visual analogue scale. This gives the HS-COPD a possibility to be used as a utility instrument, which has to be a generic instrument in order to compare various diseases/conditions. The value of adding Health Marker States is to increase the responsiveness of the instrument. Methodological work is ongoing at McMaster University, Hamilton, Canada. Subjects' preferences on format of the health marker states has been published [73].

## **Health-related quality of life – linguistic validations**

With a few exceptions, most questionnaires have been developed in English. There are many examples in the literature of the translation of HRQL questionnaires, but few publications describe the guidelines to be followed [74-76]. In recent years a standardised procedure has been worked out, comprising three main steps. The first step is the production of a culturally and linguistically adapted version of the source questionnaire. The second step is the comparison of the source and the target versions. The third step is the comparison of all target versions (international harmonisation). Each translation should follow the same established forward-backward translation procedure, with independent translations and counter-translations [75, 76].



The translation of the Asthma Quality of Life Questionnaire into different European languages is described here. C Acquadro and colleagues at the Mapi Research Institute, Lyons, France, have developed the procedures mentioned below especially for HRQL and other PROs [77]. The first step comprises two independent translations, which are then reconciled to form one version (step 2). Two translators whose native language is English then translate this version back into English. The back-translations are compared with the original and if required, the translated version is adjusted. This version, called the pre-final version, is then tested on a small number of subjects (approximately ten) with asthma in order to assess the comprehensibility and acceptability of the translation. An international harmonisation of the new version with other translated versions (if any exist) is then performed (step 3). Following any necessary adjustments, the final version is then ready for validation in a clinical study. The procedures will be the same for all translations of the AQLQ and for all instruments developed by EF Juniper. The Mapi Research Institute in Lyons, France, conducts all the linguistic validations/cultural adaptations with EF Juniper, the developer of the AQLQ, and acting as a consultant and, if possible, present during testing in subjects with asthma. The next step is to perform a validation study for each translation, either as separate studies or using data from a clinical study in which the various versions are included. The linguistic validation, including an international harmonisation of various versions, will support the inclusion of a questionnaire in a multinational study.

### **Health-related quality of life in COPD**

There are at least three ways in which an HRQL questionnaire can be used, namely as an *evaluative, discriminative or predictive* measure. Until now, there have been fewer publications of studies in COPD using HRQL questionnaires than of studies in asthma. However, the amount of research in COPD is increasing. A recent review addresses evidence of HRQL measurements in COPD [56].

The number of publications on the use of HRQL questionnaires to measure the effect of interventions is increasing (*evaluative measure*). The term *evaluative* means that the instrument has the ability to detect within-subject changes over time that occur either spontaneously or as a result of treatment or other intervention.

COPD is a disease characterised by a faster decline in FEV<sub>1</sub> than the physiological decline with increasing age that occurs in healthy subjects [1, 78]. Similar results in decline have been seen using an HRQL assessment. In the three-year long ISOLDE study with placebo as comparative treatment a yearly decline of 3.2 units in HRQL using the SGRQ was noticed [79, 80]. After treatment with the inhaled corticosteroid, fluticasone, it was shown that there was a significant reduction in the rate of decline in SGRQ.

One study reported benefits in HRQL after treatment with the long-acting  $\beta_2$ -agonist salmeterol compared with placebo and compared with ipratropium [81]. Another study reported improvements in HRQL after salmeterol treatment compared with placebo [82]. In that study, a benefit in HRQL with salmeterol 50  $\mu\text{g}$  was seen, while a higher dose, salmeterol 100  $\mu\text{g}$ , did not give any gain in HRQL. The suggested explanation was increased side effects with the high dose [82]. Adding salmeterol to theophylline was beneficial in HRQL compared with theophylline alone [83]. In a study in patients requiring additional therapy besides ipratropium, formoterol was compared with salbutamol [84]. No benefit was seen in HRQL; however, it was concluded that the study was probably too short to allow full manifestation of the effects of treatments on HRQL. In a three-month study, two doses of formoterol and ipratropium were compared with placebo [85]. Compared with placebo, formoterol 12  $\mu\text{g}$  gave a difference that exceeded the four-point difference in SGRQ total score that is considered to be clinically relevant, whereas the higher dose of 24  $\mu\text{g}$  did not reach this level.

The new combination treatments have all shown benefits in patients' well-being. In one study the combination of fluticasone and salmeterol was given and compared with each of the components, fluticasone and salmeterol, and with placebo [86]. Only the combination group showed a clinically significant improvement in HRQL using the SGRQ (mean change from baseline in total scores was -4.5). Two studies using the combination of budesonide and formoterol have been published [87, 88]. These studies demonstrated statistically significant improvements in mean SGRQ total scores for budesonide/formoterol versus placebo and formoterol. During the study by Calverley et al., as early as in run-in, where the patients were treated with prednisolone and formoterol, there was a clinically meaningful improvement from baseline (mean reduction of  $\geq 4$  units) in SGRQ total scores, which influenced the extent and significance of subsequent treatment-related changes. After the one-year treatment with budesonide and formoterol, the difference versus placebo was not only statistically significant but also clinically relevant (mean difference of 7.5 in SGRQ total score). Improvements in SGRQ total scores during the randomised treatment period were associated with fewer exacerbations and were correlated closely with reductions in symptom scores, though poorly with lung function [88]. Some papers include evaluation of HRQL after rehabilitation programmes [89, 90].

The usage of HRQL questionnaires as a *discriminative* measure in COPD has been considered. This means that a questionnaire has the ability to differentiate between subjects, or groups of subjects, with different levels of impairment, i.e. those with mild, moderate or severe impairment of HRQL. One group of researchers [91] showed that many subjects are not likely to visit their doctor until their HRQL is heavily affected. It has been shown that subjects using long-term oxygen therapy have substantially impaired HRQL [92, 93]. It has also been shown that there is closer correlation between dyspnoea and HRQL than between lung function and HRQL [94].

A *predictive* measure can be explained as having the ability to predict a future event or disease prognosis. The option of using HRQL questionnaires as a *predictive* measure is demonstrated in a study where poor scores on the SGRQ were associated with rehospitalisation for COPD and increased use of resources, such as nebulisers [95]. Another study concluded that improving physical performance and teaching adequate coping strategies should be considered in order to improve HRQL [96]. Recent data from subjects undergoing lung volume reduction surgery show that a severe deterioration in SGRQ scores seems to predict operative mortality (Löfdahl, C-G – personal communication).

In summary, HRQL questionnaires in COPD may have a value to evaluate changes after intervention. Few data exist on the use of HRQL assessments as discriminative and predictive measure in COPD.

### **Health-related quality of life in asthma**

The use of an HRQL questionnaire as an *evaluative* measure in asthma is increasing. Below, a number of published papers will be presented that include HRQL questionnaires and its use as an evaluative measure.

The regular use of inhaled corticosteroids instead of only the frequent use of short-acting  $\beta_2$ -agonists has been shown not only to give benefits in lung function but also to improve patients' well-being. Treatment with fluticasone as well as budesonide, two commonly used inhaled corticosteroids, gave improvements in HRQL in a number of studies [97-103].

The long-acting  $\beta_2$ -agonists have also been shown to improve the HRQL of asthmatic subjects. Salmeterol given twice daily resulted in significant improvements in subjects' HRQL [39, 82, 104-107]. In another study (the FACET study), adding formoterol, a long-acting  $\beta_2$ -agonist, to a high dose of corticosteroids

(budesonide 800 µg twice daily) had a small effect on HRQL using the AQLQ as well as on other traditional clinical efficacy variables [60]. The relationship between the AQLQ and other clinical efficacy variables was weak, as in other studies [39, 108, 109]. In a second study, adding formoterol to budesonide, improvements in HRQL were again seen [110].

A recent addition to the medication available for the treatment of asthma is the fixed combination of drugs. The combination of salmeterol and fluticasone has been shown to provide benefits in HRQL compared to each of the components alone [111]. Other data that support the HRQL benefit of fixed combination drugs compared with corticosteroids have been published [112].

In another fixed combination of drugs, formoterol together with budesonide is used. In a long-term safety study, this combination improved HRQL in subjects whose asthma was considered to be well controlled [113, 114].

To define asthma using HRQL as a descriptor of the disease is as difficult as in COPD. Subjects with well-controlled asthma may not differ much from healthy subjects with regard to their HRQL. However, the severity of the disease may vary over time, making it possible to use HRQL questionnaires as a *discriminative* measure. In one study, two generic (SF-36 and PGWB, Psychological General Well-being Scale) and two disease-specific questionnaires (AQLQ and LWAQ) were used to establish their ability to discriminate between asthma severity [115]. The AQLQ was shown to discriminate better than the LWAQ and the SF-36 performed better than the PGWB and the LWAQ. However, the discriminative use of these questionnaires has not currently been extensively studied and further research on between-subjects and within-subject variability is needed.

The possibility of carrying out HRQL assessments as a *predictive* measure for subjects' well-being in asthma is under evaluation. Disease severity has long been evaluated using spirometry tests with FEV<sub>1</sub> expressed as per cent of predicted as the outcome of subjects' intervention. The GINA guidelines as well as other guidelines, such as the ATS and the BTS guidelines, have used FEV<sub>1</sub>% predicted to differentiate the degree of the asthma severity [4, 116]. In the last few years it has become apparent that it is important to evaluate the burden of the disease of the subjects and to do this in a standardised way. The correlation between spirometry tests, other clinical indices and HRQL will be highlighted in the results section.

In summary, using HRQL questionnaires in asthma as an evaluative measure is increasing, whereas the use of HRQL questionnaires for discriminative and predictive purposes in asthma has to be further examined.

## AIMS OF PRESENT STUDIES

The overall aim was to study the value of using health-related quality of life (HRQL) assessments in COPD and asthma.

The aims in detail were:

1. To study the burden of completion (feasibility) of self-administered questionnaires
- 2a. To study the use of HRQL measures for evaluative purposes after pulmonary interventions in chronic obstructive pulmonary disease (COPD)
- 2b. To study the use of HRQL measures for evaluative purposes after pulmonary interventions in asthma
- 3a. To study HRQL assessments in COPD as a discriminative measure, in particular with regard to its relationship to other clinical indices and to disease severity
- 3b. To study HRQL assessments in asthma as a discriminative measure, in particular with regard to its relationship to other clinical indices and to disease severity

## INSTRUMENTS USED FOR ASSESSMENT OF HRQL

The methods employed in the present studies are described in each of the publications and will be summarised below. The clinical studies were performed in accordance with the principles stated in the Declaration of Helsinki. The final study protocols, including the final version of the Patient Information and Consent Form(s), were approved by local Ethics Committees before the enrolment of any subject in the study.

Seven PRO questionnaires were included in five papers and are presented below.

In paper I (feasibility study) the following five questionnaires were included: the generic SF-36 [42, 43], the specific SGRQ [31, 55], the preference-based EQ-5D [67], a new preference-based measure, the Health State-COPD (HS-COPD) [73], and a productivity measure, the Working Productivity and Activity Index for COPD (WPAI-COPD). The last two questionnaires are still under development. The subject population had the diagnosis COPD.

Paper II (COPD interventional study) reports an analysis from an interventional study where subjects with COPD were included and the St George's Respiratory Questionnaire (SGRQ) was used [31].

Paper III (asthma interventional study) contains analyses from an interventional study performed in adult subjects with asthma. The Asthma Quality of Life Questionnaire (AQLQ) was used in this study [59].

Papers IV-V (COPD severity study and asthma severity study) include data from two cross-sectional studies of which one was performed in Sweden in COPD subjects and one in Hungary in asthma subjects. These papers include analysis of three questionnaires, all included in the two studies. These are the generic SF-36 [43], the



specific SGRQ [31] and the preference-based EQ-5D [67]. Paper V also contains a direct TTO question and a calculation of SF-6D, which is derived from the SF-36.

All seven questionnaires were administered in self-administered versions. A standardised procedure was used for the administration. The subjects filled in the questionnaires at all visits, before any study-related procedures took place (if any) and after brief instructions from the administrator responsible. The questionnaires were also filled in for training purposes at an enrolment visit (before run-in, in papers II and III) although the results from this visit were not used in the analysis.

All questionnaires were translated and culturally adapted (linguistic validation) into the languages needed for the studies. The first study (Paper I) was performed in Sweden and Swedish versions of the SF-36, SGRQ, EQ-5D, WPAI-COPD and HS-COPD were used. The second study (Paper II) was also performed in Sweden and a Swedish version of the SGRQ was used. The third study (Paper III) covered four countries: Sweden, Norway, the Netherlands and Greece, and corresponding translations of the AQLQ were used. Native English persons developed both the SGRQ and the AQLQ and English is therefore the original language of these questionnaires. Each translation followed the same established forward-backward translation procedure, with the independent translations and counter-translations recommended [75, 76, 117].

The SGRQ was adapted for Swedish conditions following the translation-backtranslation procedure. Psychometric and clinical evaluation was then performed, and the results were published by Engström and colleagues [118]. Significant and close correlations were found between the Swedish SGRQ and the generic questionnaire, the SIP. Modest correlations were found with spirometry measures. A satisfactory internal consistency of reliability was obtained for the Swedish SGRQ. There was also good agreement between the correlation patterns in the baseline data and in a follow-up twelve months later. In conclusion, the Swedish

version of the SGRQ proved to be reliable, valid and comparable with the original English version.

The linguistic validation of each version of the AQLQ has followed the procedures presented in the introduction part. The MAPI Research Institute in Lyons, France, performed all the linguistic validations of the AQLQ, including the versions used in the present study. Elizabeth F Juniper, the developer of the AQLQ, was involved in all steps of the linguistic validation.

The SF-36 and the EQ-5D were used in studies presented in papers I, IV and V and the Swedish and Hungarian translated and culturally adapted versions were used.

Paper I included two additional questionnaires, the HS-COPD and the WPAI-COPD, which are both still under development, and Swedish translations were used.

## PATIENT POPULATION AND STUDY DESIGN

The following is a brief summary of the population and study design, which are presented in detail in Papers I-V.

Paper I assesses the burden of completion (*feasibility*) of questionnaires by subjects. The outcomes of the next two papers (Papers II and III) show the possibility of using HRQL assessments, both for *evaluative* and *discriminative* purposes.

The last papers (Papers IV and V) show how HRQL questionnaires can be used as *discriminative* measure with regard to disease severity in the two diseases, COPD and asthma.

## Paper I – Feasibility study

The aim was to study the burden (feasibility) of completion of questionnaires. The study contains data from a Swedish cohort of 174 subjects with COPD. Table 4 shows the subject characteristics. The study was performed in a three-month period during the winter of 2000 in the northern part of Sweden. After brief instructions, subjects completed five questionnaires, all in the same order, namely SF-36, EQ-5D, SGRQ, WPAI-COPD and HS-COPD. Subjects rated questionnaires for ease/difficulty of completion on a scale of 1-5 (1=very easy, 2=easy, 3=acceptable, 4=difficult and 5=very difficult). In addition, the administrator gave her opinion of how she felt about the subjects' comprehension of the instruments using a 4-point scale (1=good understanding, 2=probably understood, 3=possibly understood and 4=did not understand).

**Table 4.** Subject characteristics in feasibility study and COPD severity study

Number of subjects	174
Women / men	70 / 104
Age, years	
Mean $\pm$ SD	64.3 $\pm$ 12
Range	28 - 80
FEV <sub>1</sub> , L	
Mean $\pm$ SD	1.76 $\pm$ 0.78
Range	0.46 - 4.12
FEV <sub>1</sub> , % predicted <sup>1)</sup>	
Mean $\pm$ SD	62 $\pm$ 20
Range	18 - 118
GOLD classification	
Number of subjects:	
Stage I	19
Stage II	82
Stage III	32
Stage IV	9

<sup>1)</sup> [119]

## Paper II – COPD interventional study

### *Effects of overall HRQL in COPD and its relationship to other clinical indices*

The aim was to study the evaluative effect with HRQL assessments as well as the relationship between HRQL and other measures of airway calibre. The COPD interventional study consisted of 183 subjects with moderate to very severe COPD, comparing formoterol, ipratropium and placebo and was performed 1997–98 in Sweden. Assessments such as HRQL, symptoms, lung function and walking distance (shuttle walking test, SWT) were performed at baseline and after a three-month treatment period. Table 5 shows the baseline characteristics of the subjects.

**Table 5.** Subject characteristics in COPD interventional study given by treatment; gender and smoking habits as proportion of subjects, other variables: mean (range)

	<b>Formoterol Turbuhaler</b>	<b>Ipratropium bromide pMDI</b>	<b>Placebo</b>
Number of subjects	61	62	60
Women/men (no.)	28/33	28/34	30/30
Smoking habits (current/former)	24/37	11/51	19/41
Age, years	64 (48-74)	65 (50-74)	64 (47-74)
COPD symptoms, years	10 (1-34)	10 (1-23)	11 (2-30)
Reversibility, % pred. After ipratropium bromide	6 (-13-12)	6 (-11-12)	6 (-1-11)
Reversibility, % pred. After formoterol	6 (-2-11)	7 (0-12)	6 (-0-11)
Shuttle walking test, m	319 (70-670)	324 (90-710)	333 (60-670)
FEV <sub>1</sub> , L	0.84 (0.4-2.0)	0.87 (0.4-1.8)	0.82 (0.3-2.1)
FEV <sub>1</sub> , % predicted	33 (15-61)	34 (15-58)	33 (12-56)
SGRQ total score, 0–100	46.1 (11.6-74.5)	48.0 (14.3-79.9)	46.5 (20.3-82.1)

Changes after treatment using HRQL assessment (SGRQ) were calculated. Correlations between HRQL assessments and the other clinical measures were calculated.

### **Paper III – Asthma interventional study**

#### ***Effects of overall HRQL in asthma and its relationship to other clinical indices***

The aim was to study the evaluative effect with HRQL assessments obtained before and after treatment with two different bronchodilators used on demand. The HRQL assessment as a discriminator was examined by calculation of correlation coefficients with other clinical measures. The asthma interventional study consisted of 362 subjects with asthma and lasted three months. Two  $\beta_2$ -agonists, the long-acting formoterol and the short-acting terbutaline, both used 'on demand', were compared. The baseline characteristics of the subjects are given in Table 6.

The assessments included the AQLQ questionnaires as measure of HRQL, diary recordings of symptoms, and lung function. Changes after the treatments using HRQL assessments (AQLQ) were compared. Correlations between HRQL assessments and the other clinical measures were calculated.

**Table 6.** Subject characteristics in asthma interventional study, given by treatment  
Values are presented as means (ranges).

<b>Variable</b>	<b>Formoterol</b>		<b>Terbutaline</b>	
Number of subjects	182		180	
Women/men, no.	94/88		111/69	
Age, years	46	(18-70)	48	(18-75)
Duration of asthma, years	16	(1-66)	17	(1-60)
FEV <sub>1</sub> , L	2.36	(1.13-4.30)	2.27	(1.00-4.65)
FEV <sub>1</sub> % predicted	73.7	(4-162)	74.2	(40-130)
Reversibility, % from baseline	19	(2-77)	19	(-3-98)
Inhaled daily steroid dose, µg	890	(200-2800)	860	(100-2400)
AQLQ, score 0–7				
Overall	4.90	(1.9-6.9)	4.82	(2.3-6.6)
Activity limitation	4.82	(1.7-6.9)	4.67	(1.6-6.9)
Symptoms	4.81	(1.2-7.0)	4.75	(2.1-7.0)
Emotional function	5.35	(1.2-7.0)	5.35	(1.6-7.0)
Environmental exposure	4.85	(1.5-7.0)	4.78	(1.5-7.0)

## Paper IV – COPD severity study

The aim was to study the discriminative possibility of using HRQL assessments related to disease severity in COPD. This cross-sectional study contains data from a Swedish cohort of 174 subjects with COPD (the same cohort used in Paper I, feasibility study). The study was performed in a three-month period during the winter of 2000 in the northern part of Sweden. Table 4 shows the subject characteristics (see paper I). In this study the subjects were divided into four severity groups according to FEV<sub>1</sub>% predicted using two different clinical guidelines, the GOLD and BTS guidelines. Table 7 shows the GOLD and BTS criteria.

**Table 7.** Criteria for disease severity in COPD

<b>Global Initiative for Chronic Obstructive Lung Disease, GOLD [2]: FEV<sub>1</sub>/FVC &lt;70%</b>		
I:	Mild COPD	FEV <sub>1</sub> ≥80% predicted
II:	Moderate COPD	FEV <sub>1</sub> 50-<80% predicted
III:	Severe COPD	FEV <sub>1</sub> 30-<50% predicted
IV:	Very severe COPD	FEV <sub>1</sub> <30% predicted
<b>British Thoracic Society, BTS [4]: FEV<sub>1</sub>/VC &lt;70% and FEV<sub>1</sub> &lt;80% predicted*</b>		
I:	Mild COPD	FEV <sub>1</sub> 60-<80% predicted
II:	Moderate COPD	FEV <sub>1</sub> 40-59% predicted
III:	Severe COPD	FEV <sub>1</sub> <40% predicted

\*A group labelled BTS stage 0 was created for subjects with FEV<sub>1</sub> ≥80% predicted, i.e. identical with mild COPD according to the GOLD criteria.

Age, gender, smoking status and socioeconomic group were regarded as confounders. Three HRQL questionnaires completed by the subjects – the SF-36, the SGRQ and the EQ-5D – were compared.

## Paper V – Asthma severity study

The aim was to study the discriminative possibility of using HRQL assessments related to disease severity in asthma. The study was performed in Hungary. Table 8 shows the subject characteristics. The study consisted of 228 subjects with asthma and was of a cross-sectional design. The level of disease control was determined using GINA guideline criteria (Table 9). The term 'asthma control' is used when subjects are classified into severity groups after treatment. Three HRQL questionnaires were completed by the subjects – the SF-36, the SGRQ and the EQ-5D. A direct TTO question was also answered. Utility values were compared using EQ-5D and SF-6D, the last was derived from SF-36 [69].

**Table 8.** Subject characteristics in asthma severity study

Number of subjects	228
Women/men, no.	150/78
Mean age, years	49
GINA: Severe patients, no.	46
GINA: Moderate patients, no.	82
GINA: Mild patients, no.	64
GINA: Intermittent patients, no.	36
FEV <sub>1</sub> % predicted, mean value	71.9



**Table 9.** Criteria for disease severity in asthma

Global Initiative for Asthma (GINA) classification system [16]

	<b>Intermittent</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
PEF (%)	≥80	≥80	60<PEF<80	≤60
PEF variance	Less than once a week	More than once a week but not every day	Every day	Frequent symptoms
Night symptoms	≤2 times a month	>2 times a month	< once weekly	Continuous
Other signs/ symptoms			Use of β <sub>2</sub> -agonists Limited activity during symptoms	Frequent exacerbations

## STATISTICAL METHODS

### Paper I – Feasibility study

In paper I, data were analysed using a linear model with factors for gender, disease severity and socioeconomic group and with age as covariate. The GOLD guidelines were used for classification of disease severity. Pearson's correlation coefficients were calculated using baseline data.

### Paper II – COPD interventional study

The scores from the SGRQ were compared between treatments using an additive ANOVA model with treatment and centre as factors and with the run-in mean as a covariate [120]. The proportions of subjects with an improvement (decrease of ≥4% units), impairment (increase of ≥4% units) or unchanged condition were compared between treatment groups with a Pearson's  $\chi^2$  test. The last-value-carried-forward principle was used to estimate missing values. Correlations were investigated using scatter plots with superimposed linear regression lines. Correlation coefficients were computed with 95% confidence intervals.

### **Paper III – Asthma interventional study**

The change in AQLQ from start to end of treatment was compared between treatment groups using an analysis of variance model (ANOVA) with treatment and centre as fixed factors and the AQLQ baseline value as a covariate [120]. The mean difference and 95% confidence limits between treatments were calculated. Associations between changes in AQLQ between baseline scores and end of treatment scores and changes in conventional clinical indices were examined using Pearson's correlation coefficient. The analysis was based on all subjects with HRQL data available after randomisation. The last-value-carried-forward principle was used to estimate missing values.

### **Papers IV and V – COPD and asthma severity studies**

The following two papers (IV and V) included data from two cross-sectional studies.

In paper IV, the Mantel-Haenszel chi-square model with a significance level of 5% was used [121]. Data were analysed according to COPD staging from GOLD and BTS guidelines, using FEV<sub>1</sub>% predicted. Age, gender, smoking status and socioeconomic background were used as confounders. Multiple linear regression analyses were performed to study the differences in HRQL.

In paper V, mean values for the different HRQL questionnaires were calculated for four disease groups according to GINA. Pearson's correlation coefficients were used to express the correlation between the different HRQL measures.

## RESULTS

### **Paper I – Feasibility study**

A score of 1-3 ('very easy' to 'acceptable') was recorded by 92% of the subjects for SF-36, by 90% for SGRQ, by 83% for WPAI-COPD, by 80% for EQ-5D and by 53% for HS-COPD. 10-15% of the subjects found the SF-36, SGRQ and EQ-5D 'very easy to complete', with only 3-4% finding these questionnaires 'very difficult' to complete. Age correlated significantly with the degree of the subject's opinion of the ease of completion of five instruments, while the influence of gender, socio-economic status and disease severity was not statistically significant. The mean time to complete all questionnaires was 39 minutes.

The administrator's opinion of the subjects' understanding was generally good, with only two subjects graded as having 'not understood'.

In conclusion, the majority of subjects with COPD were able to complete up to five PRO instruments. Only age correlated with difficulty in completing the questionnaires.

### **Paper II – COPD interventional study**

The results showed little or no improvement in SGRQ total, regardless of treatment. Both active treatments significantly improved lung function and daytime dyspnoea compared with placebo. No statistically significant differences in walking distance in the SWT were found between the treatments.

Moderate cross-sectional correlations were found at baseline between the SGRQ total and symptoms, as well as between the SGRQ and SWT (in relation to breathlessness:  $r=0.67$ , cough:  $r=0.48$ , and SWT:  $r=-0.51$ ). The cross-sectional correlation coefficients of baseline values between the SGRQ total and lung function were moderate to low (FEV<sub>1</sub>:  $r=-0.28$ , and FVC:  $r=-0.16$ ). After study completion, the

cross-sectional correlation coefficients between the SGRQ total and other clinical measures were similar to those seen at baseline. Regarding changes in SGRQ total and changes in symptoms, SWT and lung function, all longitudinal correlation coefficients of change were lower than between the absolute values. The highest value was seen between change in SGRQ total and change in one of the symptom scores, breathlessness ( $r=0.34$ ).

The conclusion of this short-term study comparing bronchodilators with placebo, no effects on HRQL were seen related to treatment and therefore the evaluative effect with the HRQL assessment was unclear. In a cross-sectional evaluation, limitation in walking distance (SWT) and symptoms seem to be related to the HRQL of subjects with moderate to very severe non-reversible COPD, however, with a great individual variation.

### **Paper III – Asthma interventional study**

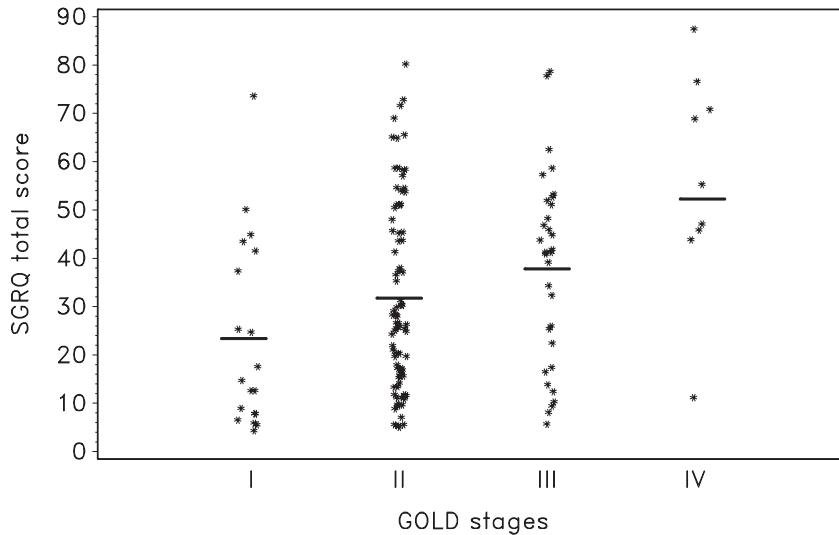
Significant improvements were seen in all assessments. Formoterol, the long-acting  $\beta_2$ -agonist used 'on demand', showed greater improvements in all measures than terbutaline, the short-acting  $\beta_2$ -agonist, did. The improvement in AQLQ overall was 0.41 in the formoterol group compared with 0.17 in the terbutaline group ( $p=0.0003$ ). The greatest improvements were seen in the symptom domain of the AQLQ, with changes of 0.49 in the formoterol group and 0.21 in the terbutaline group ( $p=0.002$ ). The number needed to treat (NNT) is defined as the number of subjects that need to be treated in order for one subject to benefit. Using AQLQ overall, the minimal clinically relevant improvement of 0.5 will be used. The NNT for the formoterol group was 9.1 with regard to the AQLQ overall and 7.7 for the symptom domain of the AQLQ. The cross-sectional correlation coefficients of the baseline values between AQLQ overall and symptoms were moderate (day:  $r=-0.37$  and night:  $r=-0.29$ ). The cross-sectional correlation coefficient between AQLQ overall and FEV<sub>1</sub> was low ( $r=0.15$ ).

The conclusion of this paper was that formoterol, when used as 'on demand' medication, provides a greater improvement in asthma-specific HRQL than the currently used rescue medication, terbutaline. The symptom domain of the AQLQ showed the greatest improvement with an almost clinical relevant change of 0.5. Thus AQLQ shows a possibility to be used for evaluative purposes in this study, whereas the relation to lung function was low.

#### **Paper IV – COPD severity study**

The degrees of severity according to both GOLD and BTS affected the mean SGRQ total score and EQ-5D significantly. The same result was found for SF-36 physical component summary (PCS), however, not for SF-36 mental component summary (MCS). The level of SGRQ total score varied significantly according to age, whereas no statistically significance was seen between the age groups for the SF-36 and EQ-5D. The gender comparison showed only a statistically significant difference in SF-36 PCS. No differences were noticed using any of the instruments in the non-smoker, ex-smoker and smoker groups, respectively. One observation has been noticed and that needs to be considered in the interpretation of the results: the individual scores of SGRQ total showed a great variation. Figure 1 shows the individual data including the mean values (marked with a horizontal line) in each of the GOLD stages.

**Figure 1.** Individual data (\*) and mean values (-) of SGRQ total score according to GOLD stages



In conclusion, the HRQL of COPD subjects seems to be dependent on disease severity and age. These data show a relationship between lung function and HRQL. A discriminative effect with HRQL assessment in relation to disease severity according to both GOLD and BTS may exist, however, not on an individual level.

### **Paper V – Asthma severity study**

The results showed that the differences in HRQL between the severity groups varied using the three instruments, the SGRQ, SF-36 and EQ-5D. The SGRQ total scores were consistently higher (worse HRQL) in subjects with lower asthma control (more severe disease) with a SGRQ total score of 21 in the intermittent group, 38 in the mild, 52 in the moderate, and 60 in the severe subject group. Differences between the asthma control/severity levels using SF-36 were more profound in the

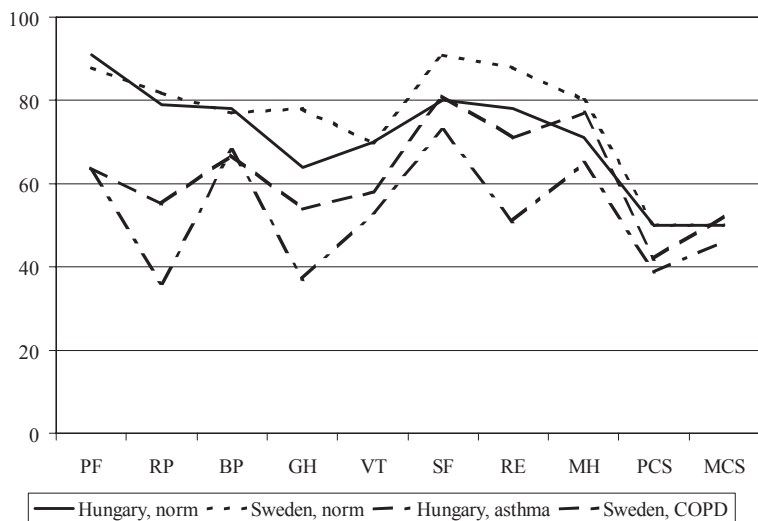
PCS score than in the mental component summary (MCS) score. Utility values gained from the EQ-5D index and SF-6D were shown to be similar in the mild to moderate groups, although the EQ-5D index was higher in the intermittent group and lower in the severe group.

In conclusion, it was shown that a low level of disease control (severity after treatment) in asthma is associated with substantial losses in HRQL. The actual pattern of the relationship between asthma control level/severity and HRQL was shown to be dependent on the measurement used. A relation between asthma severity and HRQL measurement in group comparison were seen, however, a great individual variation is likely to be seen.

### **Comparison of Papers IV and V – COPD and asthma severity studies**

In an attempt to better understand the disease burden of COPD and asthma and to compare these two respiratory diseases, the same three questionnaires that were used in the COPD population in Sweden (Paper I) and in the asthma population in Hungary (Paper IV) were compared (data not published). These questionnaires were the generic SF-36, the disease-specific SGRQ and the utility-based questionnaire EQ-5D. National normative data for the SF-36 were used to compare the results. The results suggest that both COPD and asthma significantly affect physical functioning, while mental health is less affected. Figure 2 shows the SF-36 profile for COPD and asthma, together with normative data from the two countries. The interpretation of the SF-36 summary scores should be taken with caution. The SF-36 MCS score in COPD patients shows a higher value than in the general population, despite the fact that each domain score is worse than that of the general population.

**Figure 2.** SF-36 profile of asthma and COPD patients: percentage of predicted national normative values



The eight health domains comprise physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The two summary measures are the physical component summary (PCS) and the mental component summary (MCS).

The comparison between COPD and asthma showed better HRQL in COPD patients. This trend was true for each of the HRQL measures used. The difference was most profound in the SGRQ total score, where a difference of 16 units was noticed. Asthma subjects reported more problems with usual activities or work as a result of physical health or emotional problems. One could expect that COPD patients would have a worse HRQL than asthma patients. Therefore, in the comparison between COPD and asthma, the severity of the disease in the two populations has to be considered. In the asthma population, 20% had severe asthma



according to GINA whereas only 5% of the COPD group had a very severe disease, i.e. GOLD stage IV. This may be one explanation for the low HRQL values in asthma compared to COPD. In both populations, HRQL assessments in group comparisons may be used as a discriminator for disease severity when age and gender were adjusted for. The attempt to compare the two diseases did not give any further information.

## DISCUSSION

Subjects with COPD and asthma are troubled not only by symptoms, such as breathlessness, wheezing and coughing, but also by limitations in daily activities, disturbed sleep and mental problems. When an intervention, e.g. treatment, is discussed, it is essential to *evaluate* the effects on the subjects' HRQL as well as the effects on measures of lung function. The generic questionnaires have advantages as they may be used to compare outcomes between different diseases and can also be used to evaluate the HRQL of a healthy population. Using SF-36 as a *discriminative* measure, for example, can highlight the burden for patients with various diseases. In several studies using SF-36 it has been shown that subjects with rhinitis have a lower HRQL than subjects with mild asthma and that subjects with COPD have an even lower HRQL [82, 122, 123]. However, for measuring the effect of an intervention in a population with a specific disease, questionnaires developed specifically for this disease or condition are likely to be more responsive than generic questionnaires, since they focus on the burden of that disease or condition. Both the SGRQ and AQLQ have been developed for the assessment of HRQL in asthma; however, the AQLQ has been the most widely used instrument in asthma with three times as many publications as SGRQ in MEDLINE, for example. In COPD the SGRQ is the most widely used instrument, one important reason possibly being that the other instrument in COPD, the CRQ, has not been available in self-administered format until recently.

## **Practical aspects – completion of questionnaires**

A Swedish cohort, recruited from a representative sample of the general population, completed five questionnaires, all in the following order: SF-36 [43], EQ-5D [67], SGRQ [31], WPAI-COPD and HS-COPD [73]. Few studies have been published on the feasibility of completion of questionnaires. This means that our results add information about the burden of completion of questionnaires. An Italian group for evaluation of outcomes in oncology evaluated the rate of patients not filling out an HRQL questionnaire and also the reason for it. Twelve percent did not fill out the questionnaire and the most common reasons were 'illiteracy', 'lack of glasses or poor eye-sight' and 'refusal' [124]. Other studies have compared the administration formats such as interviewer- and postal administration. Such a study by Mallinson, using the SF-36 in an elderly patient group, resulted in high levels of non-response or missing data when postal administration was chosen [125]. Electronic collection has been tested and found reliable and preferred by patients compared to paper [126].

Our study showed that subjects with COPD were able to complete the five questionnaires (SF-36, EQ-5D, SGRQ, WPAI-COPD and HS-COPD), however, with some limitations. The difference in completion between the four first questionnaires was low. A score of very easy to acceptable was recorded by >90% for SF-36 and SGRQ, followed by >80% for the WPAI-COPD and EQ-5D. One reason for difference in ease of completion may be that two of the questionnaires, namely the SF-36 and the SGRQ, were likely recognised by many subjects, and this would make them easier to complete. One limitation is the use of the WPAI-COPD and the HS-COPD, which are new instruments and still in development. Subjects may have found the last questionnaire, the HS-COPD, somewhat difficult due to the complexity of the statements used in the 'health states' that were used as guidance for the subject when considering their own 'health state'. Another limitation with the study may be the order of the instruments given to the subjects. The order used in our study was chosen in advance and may have affected the results as subjects consistently found

the first four questionnaires easy to complete, whereas the last (HS-COPD) was found to be more difficult than the others.

In our study, the mean time taken for completion of all questionnaires was 39 minutes, which can be regarded as low. Very few subjects needed more than one hour. This result may reflect the study population (northern Sweden), which have good reading skills.

The administrator's opinion of the subjects' understanding was generally good, with only two subjects graded as having 'not understood'. However, this was a subjective assessment. On the other hand, only one administrator was in charge.

Also in our study, age was correlated significantly with the decreasing ease of completion of the five instruments, whereas the influence of gender, socioeconomic status and disease severity was not statistically significant. One explanation for the latter results may be that the study was performed in Sweden, where a great majority of the population have good reading skills. Moreover, subjects with chronic diseases are often willing to complete questionnaires as they feel that the request to do so shows that their doctor or nurse cares about them. To conclude, it is possible for COPD subjects to complete up to five questionnaires.

### **Evaluative studies**

Regulatory authorities, mainly the Food and Drugs Administration (FDA), have highlighted the value of using HRQL instruments to evaluate interventions. In the last few years the FDA has requested PRO results (if applicable) together with other clinical indices when evaluating new drugs. The importance of demonstrating clear benefits for subjects is emphasised, which means that a new treatment should lead to an improvement in lung function as well as improvements in subjective PRO measures. Clearly when subjects are seeking help from their doctor, what they

mention is not a decrease in lung function, but a loss of well-being, which hopefully can be translated into a worsening of HRQL.

### ***COPD***

In our COPD interventional study, the SGRQ was included and almost no change was noticed after any of the three treatments: formoterol, ipratropium or placebo. This means that the use of HRQL for *evaluative* purposes in this study was almost non-existing. As mentioned in the introduction, other studies using long-acting  $\beta_2$ -agonists have shown small effects on HRQL [82, 85]. In the present study the dose of formoterol was quite high (18  $\mu\text{g}$  twice daily) and the side effects of the treatment may provide an explanation for the lack of improvement. The dose corresponds to the high dose, salmeterol (100  $\mu\text{g}$  daily), which did not show a significant effect on HRQL [82]. Another reason for our results may be the subject population. The subjects had moderate to very severe COPD (mean FEV<sub>1</sub> 33% predicted) with low reversibility; however, the level of their baseline HRQL was rather high (mean SGRQ total score 47). Swedish subjects on the whole have ready access to the health-care system and therefore their HRQL is possibly higher than in other countries with a less developed health-care system. A further reason may be the duration of the study. The present study lasted only three months, whereas in three one-year studies, there was an improvement in HRQL using the SGRQ and after using the combination of inhaled corticosteroids and long-acting  $\beta_2$ -agonists [86-88].

In another study it has been shown that as COPD progresses, a faster decline in lung function as well as in HRQL occurs in subjects with COPD than in healthy subjects [1, 78]. The long-term ISOLDE study found a slower decline in HRQL after treatment with inhaled corticosteroids than placebo [79]. The characteristic decline in lung function may be reflected in the subjects' HRQL, and a slower decline in HRQL may be a way of assessing the outcome of an intervention. However, a slow decline of the disease allows subjects to adapt to their symptoms, explaining why some subjects still have a good HRQL despite a low FEV<sub>1</sub>. Our study was likely too short to show any change in HRQL.

To conclude, our 3-month study did not show any evaluative effect of using an HRQL assessment.

### ***Asthma***

The results for HRQL obtained using the AQLQ in our asthma interventional study show that this instrument adds *evaluative* information on the well-being of the subjects even if the change from baseline did not reach the clinically relevant improvement of  $\geq 0.5$ , which is considered to be the MID value using the AQLQ. However, the benefits of using a long-acting  $\beta_2$ -agonist instead of a short-acting  $\beta_2$ -agonist 'on demand' were seen in a statistically significant improvement in AQLQ overall scores. It has previously been shown that when adding formoterol to budesonide, an added benefit in HRQL using the AQLQ is seen [60]. Studies with another long-acting  $\beta_2$ -agonist, salmeterol, have also shown benefits in HRQL using the AQLQ [104]. Salmeterol has been recognised to be a good treatment for asthma based on HRQL in eight studies (four paired studies with a twelve-week, double-blind, randomised, placebo-controlled design). Just over 2000 subjects were enrolled, and the AQLQ was used [104-107].

In a long-term safety study well-controlled subjects (mean FEV<sub>1</sub>%  $\geq 95\%$  predicted) were given a combination of formoterol and budesonide administered in one inhaler. HRQL was measured with the MiniAQLQ [63]. After one month an improvement in score of almost 0.5 from baseline was seen, which was sustained for one year [114]. This improvement is considered to be a clinically relevant change for subjects. In another clinical study with a combination inhaler (salmeterol and fluticasone), improvements after treatment in HRQL were again seen [127, 112]. Besides using the MID, calculation of the NNT is another way to interpret the changes. In the study by Juniper et al. a clinically relevant change from baseline in AQLQ overall was seen after treatment with salmeterol/fluticasone. However, the difference between the combination of salmeterol and fluticasone and mono-therapy of inhaled corticosteroids was less than 0.5, the minimal clinically relevant difference for the

AQLQ. The NNT was 3.4, which indicates that only 3.4 patients need to be treated with this combination for one patient to experience a meaningful improvement ( $\geq 0.5$ ) in HRQL relative to monotherapy with increased doses of inhaled corticosteroids [112].

Our asthma interventional study concludes that the long-acting  $\beta_2$ -agonist formoterol used 'on demand' improves subjects' HRQL, as measured using the AQLQ, to a greater extent than the short-acting  $\beta_2$ -agonist terbutaline used 'on demand'. However, despite the statistically significant improvement, the change from baseline was 0.41 in the formoterol group versus 0.17 in the terbutaline group, and the MID did not reach a change of the MID of 0.5 from baseline, nor was there a difference between the treatments of 0.5. In our asthma interventional study the NNT was 9.1 for AQLQ overall, which means that it is necessary to treat 9 subjects to have one subject showing an improvement in AQLQ overall of  $\geq 0.5$ . The comparator in this case was the short-acting  $\beta_2$ -agonist terbutaline. The added value of formoterol is its long duration, as the fast onset of action is a benefit confirmed for both treatments. One explanation for the result may be a need for fewer doses from the inhaler that was used. It may be that the onset of symptoms, as a reminder of the need for treatment before taking a dose, decreases the HRQL of the patients. The NNT in other indications shows the added value of using it. In a study in diabetes, the NNT for an important increase in HRQL after receiving a new treatment was calculated to be 10 [128]. The benefit in HRQL of immunotherapy versus injection of adrenalin in preventing allergic reactions after insect stings generated a NNT of 1.4 [129]. Another example where the NNT clearly could be much higher is the benefit of hypertension treatment, which showed a reduction in cardiovascular mortality of 17%, and with the NNT of 282 subjects one death will be avoided [130].

In summary, using the AQLQ may be used for evaluative purposes in asthma even in relatively short-term studies.

### **Discriminative value of HRQL assessments**

Using HRQL as a *discriminator* seemed to be clearer in COPD than in asthma when comparing the studies in the present thesis. One possible reason is the study population of subjects with COPD. Only subjects in Sweden were recruited for the analysis in papers II and IV (COPD subjects), whereas the asthma subjects presented in paper III and V were from various European countries and several physicians and regions were involved. The instruments used also resulted in variations in the outcome. It seems that the disease-specific questionnaire may have a better discriminative effect than the generic instruments. One reason for this may be that the symptom domain will correlate with disease severity [10]. Using the MID concept to discriminate between disease severity levels may be challenged. In the COPD population the differences in the SGRQ total score were 9, 6 and 18 between the GOLD stages I-II, II-III and III-IV. The corresponding values of SGRQ total scores in the asthma population were 17, 14 and 8 using GINA stages intermittent-mild, mild-moderate and moderate-severe. However, the MID concept has not been developed for use as a discriminator for disease severity and further research evaluating this possibility is needed. Another limitation of the result is the low number of patients per group in the two severity studies.

### ***COPD***

The cross-sectional correlation coefficient for the baseline values in the interventional study between SGRQ total and FEV<sub>1</sub> was low to moderate. Moderate correlations were seen between SGRQ total and symptoms. Similar cross-sectional correlation coefficients of the absolute values were seen after treatment. When comparing the changes after treatment, the longitudinal correlation coefficients were all lower. Low correlation coefficients have been shown in other studies. In a study by Monso et al. the correlations between HRQL and lung function were in the range between -0.01 and -0.27. In that study the NHP was used with the lowest value in the 'pain' domain and the higher value in the 'physical mobility' domain [131]. Another study showed that low HRQL measured by SGRQ is associated with

readmission to hospital for COPD and also with the use of medication [95]. The correlation coefficient between SGRQ total score and FEV<sub>1</sub>% predicted was 0.07. The decline in HRQL (SGRQ total score) is also correlated with a decline in lung function (FEV<sub>1</sub>), with a coefficient of -0.24 [80].

The correlations between HRQL and other clinical indices in our COPD interventional study seemed to be similar to those seen in other publications. However, this was not consistent with the results from our COPD severity study in which some relationship between HRQL and lung function was seen.

In the COPD severity study, the subjects were divided into groups according to FEV<sub>1</sub>% predicted using the GOLD and BTS guidelines. The degrees of severity were significantly related to the outcome of HRQL in a discriminative way, using SGRQ, SF-36 and EQ-5D. Age affected the subjects' level of HRQL as well. None of gender, smoking status or socioeconomic group gave significant differences in HRQL using any of the questionnaires. Some relationship between lung function and HRQL was shown. A moderate association between HRQL and FEV<sub>1</sub>% predicted has been seen in another study; however, a large variation in deterioration was observed within each severity stage, indicating that both lung function measures and HRQL measures should be considered in the assessment of patients in COPD [132]. In another study a relationship between HRQL and disease severity (GOLD stages) was seen in patients in GOLD stages III and IV but not in stages 0 to II [133]. However, in the majority of studies the correlation between lung function and HRQL has been shown to be weak [134, 135]. One reason for the better correlation between lung function and HRQL in our COPD severity study may be the effect of the psychosocial variable on the HRQL outcome [135]. The subjects in our severity study seemed to have a better HRQL score compared with other subject groups with a similar level of lung function. In our COPD interventional study, all subjects had moderate to very severe disease according to GOLD. In addition, all relationships between lung function and HRQL were calculated using the complete subject group in the interventional study and were weak both before and after treatment. There is



one study that supports the results of our COPD severity study. That study showed that the association between lung function and HRQL can be predicted by perceived self-efficacy for functional activities [136]. It was also suggested that both medical and psychosocial influences should be considered in order to provide adequate assessment and treatment.

The possibility of using HRQL assessments as a *predictor* for morbidity is another aspect to consider. In our COPD severity study, a great individual variation was seen within groups defined on the basis of FEV<sub>1</sub>. It is highly probable that the severity of deterioration of HRQL has an additive predictive value despite lung function measures. One possibility for the future could be to use a combination of clinical measures which has been suggested by Celli and colleagues [137]. A combined score, the BODE index, includes the body-mass index (B), the degree of airflow obstruction (O), dyspnoea (D), and exercise capacity (E) measured by the six-minute walking test. The BODE index has been shown to be better than FEV<sub>1</sub> at predicting the risk of death from respiratory causes among patients with COPD [137]. The BODE index does not include any HRQL assessments which may be limitation, however, a PRO instrument on dyspnoea is included.

### ***Asthma***

The Pearson cross-sectional correlations of baseline data from the interventional study were low between AQLQ overall and FEV<sub>1</sub> ( $r=0.15$ ), which could be expected. Other publications have reported similar discriminative findings [39, 60, 108, 109, 138, 139]. Comparing the four countries Sweden, Norway, the Netherlands and Greece, the cross-sectional correlation coefficients for baseline values between AQLQ overall and FEV<sub>1</sub> were all low, ranging from -0.11 (the Netherlands) to 0.17 (Norway). The cross-sectional correlations of baseline data for AQLQ overall and symptoms (day and night) were higher (day  $r=-0.37$ , night  $r=-0.29$ ) despite the fact that the AQLQ includes a symptoms domain. In the four countries, the correlation coefficients of AQLQ overall and daytime symptoms varied from -0.55 to -0.35, which is in the same range as seen in other publications [60, 108]. One possible

explanation for the moderate correlation between AQLQ and symptoms may be that AQLQ includes not only a symptom domain but also domains of activity limitation, emotional function and exposure to environmental stimuli.

The asthma severity study included subjects with asthma, who were divided into disease severity/control level according to GINA. All instruments used were able to *discriminate* between different severity/control levels. A similar result for the relationship was seen; however, the pattern of the relationship depended on the instrument used. The SGRQ seemed to discriminate between the severity/control levels to a larger extent than the other two instruments. This may be due to the disease-specific questions included in this instrument.

Compared with the SF-6D results, the EQ-5D index gave a substantially higher mean value in the case of the least severe asthmatics and gave a substantially lower mean utility value in the case of the patient group with the lowest asthma control level. The results highlight that the SF-6D instrument suffers from the 'floor effect problem' whereas the EQ-5D index suffers from the 'ceiling effect problem'. In other words, the discriminative validity of the SF-6D instruments is limited among patients with severe disease and the EQ-5D index is limited among patients with very mild disease. The most probable reason for the ceiling effect of the EQ-5D index is that it contains only three levels. The SF-6D instrument, on the other hand, has 4-6 levels, depending on the questions. The ceiling and floor effects from the EQ-5D index and SF-6D, respectively, have been noticed in a study by Kopec et al [140]. In another study comparing various utility measures, again the EQ-5D index showed a ceiling effect [141]. The EQ-5D index and SF-6D results were comparable in patient groups with mild to moderate control level. As preference weights for the SF-6D method were elicited by the standard gamble method, whilst the TTO method was used to elicit preferences for the EQ-5D instrument, it was expected that the SF-6D would give generally higher scores. In a publication by Green et al, a review of utility studies concluded that the standard gamble method results in higher scores than the TTO method [142]. This result suggests that in

mild and moderate asthma, the EQ-5D and the SF-6D are likely to yield identical utility scores.

### ***COPD and Asthma***

No proper comparison between the two diseases, COPD and asthma, has been performed so far. We used the two severity studies in our comparison, one study in COPD, performed in Sweden, and one in asthma, performed in Hungary. The results indicate that the asthma patients had a worse HRQL than the COPD patients. The difficulty with this attempt to compare COPD and asthma was that the two study populations were from two countries. It means that there are at least two uncertainties; the disease and the culture. The patients were also divided into severity groups according to two guidelines, GOLD and GINA, and difference in disease severity probably affected the results as well. The percentage of patients with severe disease varied and this may be one explanation for the worse HRQL in asthma (20% within the highest GINA stage in asthma compared with 5% in the highest GOLD stage in COPD). Moreover, there was a small gender difference between the two studies, as 47% were women in the COPD study and 66% in the asthma study. In a study by Juniper et al., it was found that importance scores, i.e. the importance ratings of various aspects of life quality, tended to be higher for women than for men, suggesting that women may be more sensitive to changes in HRQL [59]. On the other hand, Malo et al. showed no gender effect in Canadian asthma patients [143]. It is well known that many COPD patients have a low HRQL, although adaptation to this disease is likely higher than in asthma, mainly due to the slow deterioration. This is another possible reason for the differences in the HRQL values. Using the national normative values for the SF-36 in the two countries, it could be seen that physical functioning deteriorates in both diseases, whereas the psychological domain was less impaired. This is not in line with recently published results showing that the psychological burden in COPD is high [144-147]. In addition, morbidity is still high in patients with asthma, despite advances in management over recent decades [148]. There has, so far, been a strong focus on documentation of symptoms and activity limitations in both diseases,

whereas the psychological and social burdens have been less studied. Research aimed at understanding the burden in both COPD and asthma is needed.

To summarize, the relationship between HRQL and lung function was low to moderate in COPD, whereas between HRQL and symptoms, the relationship was stronger. In asthma, the relationship between HRQL and lung function was low. A discriminative effect of using HRQL assessments in COPD and asthma in relation to disease severity was noticed.

## CONCLUSIONS

- The completion of up to five PRO questionnaires was well accepted by subjects with COPD.
- HRQL questionnaires might be used for evaluative purposes in COPD and asthma, although in COPD longer studies will be needed.
- HRQL questionnaires appear to have a possibility to be used for discriminative purposes in COPD and asthma, and for comparison of the diseases; however, this needs to be further explored.
- In homogeneous populations, used in evaluative studies, assessment of HRQL is valuable. In heterogeneous populations, a great variation in HRQL is likely to be seen and therefore there may be a chance to show a relationship between HRQL and lung function measures. However, within severity stages there is a great individual variation.

## IMPLICATIONS AND FUTURE DEVELOPMENT

The future evaluation of treatment of subjects with chronic airways diseases such as COPD and asthma will need to focus on their well-being using standardised HRQL questionnaires. There are disease-specific HRQL questionnaires available that have documentation on measurement properties and are recognised and accepted by respiratory societies and regulatory authorities. Linguistic validation of HRQL instruments, including cultural adaptation according to standardised methods, will support use of the instruments.

The use of preference-based utility measures will be a regulatory requirement in the near future and needs to be further explored. The EQ-5D and the calculated SF-6D have been used to a limited extent maybe due to their low sensitivity to change. For the future, the HS-COPD used in the feasibility study has undergone further development and the first part including the health states has recently been published [73]. The sensitivity of the HS-COPD seems to be better than other well-known utility measures, i.e. Standard Gamble (data on file). However, if the HS-COPD is to be regarded as a true utility measure, a population study needs to be performed. The utility concept includes an uncertainty issue and therefore the Standard Gamble (still regarded as the 'golden standard') concept needs to be linked to a new utility measure.

The possibility of using the MID concept for interpretation of outcome of HRQL results has been a challenge for a long time and still is. The term was originally defined as "the smallest difference in a score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive costs, a change in the patient's management" [149]. The MID was interpreted as 'change from baseline' after intervention and has been used to evaluate various treatments for the patient. The challenge of using the MID value between treatment groups is that in a comparison between two or more good treatments it may be difficult to differentiate between the treatments using

the MID score. Maybe the MID can be used to differentiate between disease severity in the future. In our study, the MID was used for exploratory purposes in the interpretation, however, further research confirming this possibility is needed.

There is still a lack of complete understanding of patient burden with COPD and asthma. The adaptation factor is high and patient perception of disease has not been studied in depth. There is increasing evidence that monitoring HRQL in COPD and asthma can play a useful part in clinical practice. One study involving COPD and asthma patients undergoing 537 consultations revealed that gathering information on patients' HRQL systematically and routinely before a consultation could be efficiently integrated into medical decision-making process [150]. A clear understanding of the differences in disease burden with regard to HRQL assessments in COPD and asthma is needed. A limitation of present HRQL instruments is that these are developed to assess group changes. Future research will likely focus on the individual patient and there will be a need to develop new instruments on an individualised level.

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