Fatigue, functional status, health and pulmonary rehabilitation in patients with chronic obstructive pulmonary disease

Kersti Theander
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Nog finns det mål och mening i vår färd - men det är vägen, som är mödan värd.

ur "I rörelse" från "Härdarna"

Karin Boye, 1927
ABSTRACT
Theander K. 2007. Fatigue, functional status, health and pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Linköping University Medical Dissertation No. 980 Department of Medicine and Care, Division of Nursing Science, Faculty of Health Sciences, Linköping University, SE-581 85 Linköping, Sweden. ISBN: 978-91-85715-95-4 ISSN: 0345-0082

The aim of this thesis was to describe fatigue, functional limitations due to fatigue and health in patients with chronic obstructive pulmonary disease (COPD), as well as to compare patients with individuals from the general population and to test if pulmonary rehabilitation can reduce fatigue and functional limitations, and thus improve health. A further aim was to test the Fatigue Impact Scale (FIS) among patients with COPD.

Two studies (I, II) had a descriptive comparative design with data from 36 and 151 patients with COPD respectively, and 37 and 95 individuals respectively, randomly selected from the general population. One study (III) was a randomised pre-test post-test study with 12 patients with COPD randomised to 12 weeks’ pulmonary rehabilitation and 14 patients in a control group. In a further study (IV), the FIS was tested for validity and reliability among 296 patients with COPD who reported fatigue.

Assessments: Structured questions frequency, duration and severity of fatigue, functional limitations due to fatigue with FIS, six minutes’ walking distance, hand grip strength, functional performance and satisfaction with Canadian Occupational Performance Measure and health with St George’s Hospital Respiratory Questionnaire and Short Form-36.

Almost half of the patients with COPD had a problem with fatigue every day and experienced fatigue as a severe symptom. More than 44% reported that fatigue was one of the worst symptoms. The experience of fatigue was related to the patients’ functional performance and health perceptions. Patients with COPD experienced a higher frequency, longer daily duration and greater severity of fatigue than individuals from the general population. After a 12 week pulmonary rehabilitation programme, there were no statistically significant differences between the patients randomised to the rehabilitation group and those in the control group. The patients in the rehabilitation group improved walking distances, performance and satisfaction with regard to their own selected activities compared with baseline.

Confirmatory factor analysis on the three-factor model proposed for FIS showed that the fit of the model was not acceptable. Further validation of the FIS resulted in a removal of 15 items (FIS-25) and support for Pipers’ theoretical framework of subjective manifestations of fatigue including physical, emotional and cognitive dimensions and a general behavioural factor. The internal consistency, sensitivity and stability correlations of FIS-25 were satisfactory.

In conclusion, fatigue is a major concern among patients with COPD, impacting on functioning and health. Interventions with 12 weeks’ pulmonary rehabilitation might not be effective enough to reduce fatigue and the functional limitations due to fatigue. More research is needed to solve the symptom burden of fatigue and its impact on functioning and health in patients with COPD.

Keywords: chronic obstructive pulmonary disease, fatigue, functional status, health, pulmonary rehabilitation, Fatigue impact scale, confirmatory factor analysis
ORIGINAL PAPERS

This thesis is based on the following papers, which are referred to by their Roman numerals:


II. Theander, K., Jakobsson, P., Torstensson, O., Unosson, M. Severity of fatigue is related to functional limitations and health in patients with chronic obstructive pulmonary disease. (Submitted for publication).

III. Theander, K., Jakobsson, P., Jörgensen, N., Unosson, M. Effects of pulmonary rehabilitation on fatigue, functional status and health in patients with COPD. (Submitted for publication).


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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>CFI</td>
<td>Comparative Fit Index</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COPM</td>
<td>Canadian Occupational Performance Measure</td>
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<tr>
<td>CRQ</td>
<td>Chronic Respiratory Questionnaire</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
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<tr>
<td>FAI</td>
<td>Fatigue Assessment Instrument</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume produced in first second</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat Free Mass</td>
</tr>
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<td>FFMI</td>
<td>Fat Free Mass Index</td>
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<td>FSS</td>
<td>Fatigue Severity Scale</td>
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<td>FIS</td>
<td>Fatigue Impact Scale</td>
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<tr>
<td>GOLD</td>
<td>Global initiative for chronic obstructive lung disease</td>
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<tr>
<td>MCID</td>
<td>Minimal clinical important difference</td>
</tr>
<tr>
<td>MFI</td>
<td>Multidimensional Fatigue Inventory</td>
</tr>
<tr>
<td>MLR</td>
<td>Maximum Likelihood procedure with robust estimation</td>
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<tr>
<td>PFS</td>
<td>Piper Fatigue Scale</td>
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<tr>
<td>RMSEA</td>
<td>Root Mean Square Error of Approximation</td>
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<tr>
<td>SF-36</td>
<td>Medical Outcomes Survey Short Form 36</td>
</tr>
<tr>
<td>SGRQ</td>
<td>St George’s Hospital Respiratory Questionnaire</td>
</tr>
<tr>
<td>VAS-F</td>
<td>Visual Analogue Scale for fatigue</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
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<tr>
<td>6MWD</td>
<td>6 minutes’ walking distance</td>
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ORIGINAL PAPERS I - IV
INTRODUCTION
For more than 20 years, it has been known that fatigue is the second most common symptom among patients with chronic obstructive pulmonary disease (COPD) (Kinsman et al. 1983a). However, little attention has been paid as to how fatigue impacts on functioning and health, or as to what interventions could be successful in reducing functional limitations due to fatigue.

COPD is the fifth leading cause of death and disease burden in the world (WHO 2003) and by 2020 it is expected to rise to the third position (Murray et al. 1997). In the Nordic countries the prevalence of COPD among persons 45 years or older varies between 6 and 10% (Bakke et al. 1991, Lundbäck et al. 2003) and the prevalence is increasing with age.

COPD is mainly caused by cigarette smoking. The disease often starts with chronic cough and sputum production, especially in the mornings, before the development of airflow limitations which are often ignored by the patients (Siafakas et al. 1995). The patients sometimes think this is normal aging or that they are out of condition. When forced expiratory volume produced in first second (FEV1) is < 30% of the predicted value, dyspnoea often occurs at rest and is present during daily activities such as dressing and washing, leaving the patient confined at home. Patients who suffer from dyspnoea often experience anxiety and/or depressive symptoms but the cause and effects relation is unclear (ATS 1999). The natural course of the disease is characterized by increasing events of exacerbations where the baseline dyspnoea increases (Burge et al. 2003). Traditionally, the treatment of patients with COPD has focused almost exclusively on the lungs. In recent years, COPD has been proposed to be a systemic disease causing secondary effects. Skeletal muscle dysfunction, weight loss, nutritional abnormalities and systemic inflammation are recognised systemic effects that open the way for other therapies in the management of patients with COPD (Agusti 2005).

Patients with COPD have reported that the symptom of fatigue is always present, which affects their physical, emotional and social functioning (Small et al. 1999). Fatigue has been found to have an impact on daily activities, including work, mobility, household and social life. The symptom of fatigue and its effects have been measured using questionnaires where the symptoms and the effects on daily activities have not been separated (Meek et al. 2003, Piper et al. 1989, Smets et al. 1995). A questionnaire, Fatigue Impact Scale (FIS), developed to measure the functional limitations due to fatigue (Fisk et al. 1994) in patients with multiple sclerosis (Fisk et al. 1994) and used among other groups of patients (Björnsson et al. 2004,
Ingles et al. 1999, LaChapelle et al. 1998) has not previously been used or validated for patients with COPD. Fatigue is also reported to be associated with patients’ perceptions of their health (Belza et al. 2001, Yeh et al. 2004). However it is unclear how different degrees of fatigue severity limit the patients’ functioning and impact on their health perceptions.

Nursing care is often provided in a pulmonary rehabilitation program, a multidisciplinary program of care. Improvements after pulmonary rehabilitation on symptoms including fatigue as well as functional capacity and health have been reported (Lacasse et al. 2006) but research designed to test interventions with the purpose of reducing the functional limitations due to fatigue are lacking.

This thesis will focus on perception of fatigue, functional status, health, effects of pulmonary rehabilitation and a validation of the FIS for patients with COPD.

BACKGROUND

A conceptual model

In attempt to clarify the role of possible variables influencing health and well being in patients with COPD, the revised Wilson & Clearly model of patient outcome was chosen for this thesis (Ferrans et al. 2005). The model provides a useful support for the analyses of symptoms, function and health in patients with COPD. Although this model was not explicit at the start of the thesis, the model offers a possibility of clarifying the conceptual underpinnings of the research variables and integrating the research findings (Polit et al. 2003). Models or frameworks are seen as efficient mechanisms for summarizing accumulated facts, sometimes from separate investigations (Polit et al. 2003).

Wilson and Clearly conceptualised a model of patient outcome, linking the biomedical and social science paradigms (Wilson et al. 1995), focusing both on clinical variables, functioning and well being, as well as environmental and patient characteristics. The components included in this model are: Biological and physiological variables, symptom status, functional status, general health perceptions and overall quality of life, individual and environmental characteristics, and nonmedical factors. Ferrans et al. (2005) revised the model with the intention of applying it to nursing and health care (Figure 1). Although tentative, the arrows in the model symbolize the hypothesized association between the components. The dimensions included in the model have been tested on patients with COPD (Arnold et al. 2005) and other
groups of patients, such as patients with AIDS (Sousa et al. 2006), patients with heart failure (Heo et al. 2005) and patients with Hodgkin’s lymphoma (Wettergren et al. 2004).

The revised conceptual model begins with *biological function*. Biological function is viewed broadly and encompasses molecular, cellular and whole organ level processes. The evaluation focuses on variables commonly measured in clinical practice, such as laboratory values, physical assessments and medical diagnosis. The biological function is influenced by individual and environmental characteristics. For example, genetic composition predisposes people to the development of different diseases and different attitudes influence people to make choices about lifestyle. The effects from the environment can for example be exposure to pathogens in the environment, which can cause infections. In addition, interaction between characteristics of the individual and the environment affect biological function for example smokers develop COPD but others do not (Ferrans et al. 2005).

The next component, *symptoms*, defined as “a patient’s perception of an abnormal physical, emotional or cognitive state” (p.339) (Wilson et al. 1995), such as fatigue, anxiety or
depression. The focus for evaluation of symptoms is altered from the biological to the human being as a whole. Symptoms are often measured as frequency, intensity or severity (Dodd et al. 2001). Besides the biological function, the symptoms are influenced by characteristics of the individual and the environment, for example, an individual’s knowledge about his/her disease and his/her interactions with healthcare providers influence the perception of the symptoms (Ferrans et al. 2005).

The third component, functional status, is defined as “the ability of the individual to perform particular defined tasks in multiple domains, such as physical function, social function, role function and psychological function” (p.339) (Wilson et al. 1995). Functional status is defined according to Leidy et al. (1994) to include four dimensions: Functional capacity, functional performance, functional capacity utilization and functional reserve. Functional performance can also be indirectly measured as functional impairment or limitations. Both biological function and symptoms affect functional status and are also affected by characteristics of the individual and the environment. A symptom can be severe and limit both functional capacity and performance (Ferrans et al. 2005).

General Health perceptions, the fourth component, is influenced by all the earlier components of the model and it is subjective in nature. It is a synthesis of all the various aspects of health in an overall evaluation. However, the use of the measures of the other earlier components of the model, i.e. symptoms and/or functional status, is not sufficient in order to assess general health perceptions. General health perceptions is measured by means of a single, overall question, or several items, about health (Ferrans et al. 2005).

The final component of the model, overall quality of life, is subjective well-being, related to how happy or satisfied someone is with life as a whole, which is important to him/her. Overall quality of life can be measured using an overall question, or through examining various domains of life (Ferrans et al. 2005). In this thesis, the overall quality of life is not in focus.

Patients with COPD

Biological function

COPD is a chronic progressive disease, characterized by chronic airways obstruction that is not fully reversible. The prevalence of COPD is largely dependent on age, smoking habits and criteria used for defining the disease: American Thoracic Society (ATS), British Thoracic
Society (BTS), European Respiratory Society (ERS) or Global initiative for chronic obstructive lung disease (GOLD). The criteria for the disease and the classification of disease severity according to BTS are an FEV\textsubscript{1}/VC ratio < 0.70 and decreased FEV\textsubscript{1} % of predicted, which are used in this thesis. Mild COPD represents an FEV\textsubscript{1} of 60-80% of predicted, moderate 40-59% of predicted and severe < 40% of predicted (BTS 1997). In northern Sweden, the prevalence of COPD for the general population aged ≥ 45 years is 10% according to the BTS criteria (Lindberg et al. 2005). In patient with COPD in northern Sweden, the prevalence of mild, moderate and severe disease according to BTS, is 65%, 27% and 8% respectively (Lindberg et al. 2006).

COPD is considered to be a multi component disease, with several systemic effects occurring outside of the lungs, i.e. muscle dysfunction, weight loss, nutritional abnormalities and systemic inflammation (Agusti 2005). Involuntary weight loss occurs in about 50% of patients with severe COPD and in about 25% of patients with moderate COPD (Schols et al. 1993). Body mass index (BMI), < 25kg/m\textsuperscript{2}, is reported as an independent predictor of mortality (Schols et al. 1998). In out-patients with moderate to severe COPD, depletion of fat free mass (FFM) has been reported in 20% (Engelen et al. 1994). FFM consists of water, minerals and protein and is a useful measure of body cell mass and thus the muscle mass (Schols 2003). Fat free mass index (FFMI) (FFM/height (m\textsuperscript{2}) below 16.6 has been shown to be an independent predictor of mortality (Slinde et al. 2005).

The reason for weight loss is not fully understood but a combination of poor dietary intake (Cochrane et al. 2004, Schols 2000), increased resting energy expenditure (REE) (Baarends et al. 1997) and ongoing inflammatory processes (Schols 2002) have been reported. During exacerbation, malnutrition is aggravated (Vermeeren et al. 1997). Malnourished patients with COPD have been reported to have a reduced energy intake in comparison with adequately nourished patients (Cochrane et al. 2004). Patients have described different experiences during the meal situation (Cochrane et al. 2004, Odencrants et al. 2005) that influence the food intake such as early satiety, bloated stomach, dry mouth, lack of taste and appetite. Lack of inclination to eat and the smell of food were experienced as serious problems. Dyspnoea and fatigue are described as serious problems during meals and preparation of meals. Grocery shopping; carrying, lifting and transportation of the groceries are other meal related problems. Hyper-metabolism at rest has been reported among patients with COPD (Creutzberg et al. 1998, Schols 2002).
Skeletal muscle dysfunction is common in patients with COPD, which is associated with the patients’ activity and exercise capacity (ATS ERS 1999). It is not quite clear but sedentary lifestyle is suggested to play a major role (ATS ERS 1999). Systemic inflammation, altered nutritional status (Schols 2003) and steroid treatment are other factors that may influence muscle dysfunction (Morgan 2005). Skeletal muscle dysfunction has been shown to result in reduced muscle strength and endurance, and leg fatigue. Leg fatigue is reported to limit the patients’ exercise tolerance, which for some patients is the main limiting symptom (Killian et al. 1992, Maltais et al. 1996). Changing the patients’ sedentary lifestyle with systematic muscle training could be effective.

The symptoms of fatigue
Fatigue is characterized as an abnormal or unusual perception, in contrast to tiredness, often experienced with no relation to activity or exertion (Piper 2003, Ream et al. 1996). According to Piper (2003) fatigue is a generalized, whole body experience that does not follow the circadian rhythm or it is not relieved by rest. The function of fatigue is not protective as tiredness is. When fatigue lasts for a month or more it is considered to be chronic fatigue.

Fatigue is reported to be one of the most prevalent symptoms, in patients with COPD (Gift et al. 1999, Graydon et al. 1995). However, one study defines to fatigue as only “feeling lack of energy during the past week” (Gift et al. 1999). The prevalence of fatigue, assessed as intensity or severity ranges between 43% and 58% in different studies (Jansson-Bjerklie et al. 1986, Kinsman et al. 1983a, Kinsman et al. 1983b, Walke et al. 2004). In end-stage disease, the prevalence is reported in 68% and 80% of the patients (Lynn et al. 1997, Skilbeck et al. 1998). The frequency and duration of fatigue have to a lesser extent been described for patients with COPD, as has whether fatigue is experienced as a moderate or a severe symptom.

In qualitative studies, Ream and Richardson (1997) and Small and Lamb (1999) describe that, in patients with COPD, feelings of fatigue are always present and this affects the daily living and it is unpredictable and difficult to control. Feelings of being drained of energy are described. Poor concentration, lack of “get up and go”, low motivation, irritability, frustration, depressed mood and poor self-esteem were also described. Inability to participate in social activities and imposed limitations on the patients’ everyday lives were reported (Ream et al.
small et al. 1999). In these studies, the patients describe both fatigue and the impact of fatigue on daily living with behavioural, physical, cognitive and emotional manifestations.

Fatigue is a frequent symptom experienced by different groups of patients (Ekman et al. 2002a, Karlsen et al. 1999, Lerdal et al. 2003, Tsay 2004). In primary care, fatigue was present in 14% of the patients and was the major complaint in 7% of the patients (Cathebras et al. 1992).

Fatigue and vitality are concepts that are related to each other. Vitality is the positive feeling of energy (Ryan et al. 1997). In a health status questionnaire, Medical Outcomes Survey Short Form 36 (SF-36), vitality is described as feelings of energy, pep, tired and worn out (Ware et al. 1992). Vitality is therefore described as a continuum from full of energy to worn out.

Fatigue is not unusual among the general population (Aaronson et al. 2003, Bultmann et al. 2002, Glaus et al. 1996, Loge et al. 1998). The prevalence of substantial fatigue is reported to occur in 11% and 20% in the community (Bultmann et al. 2002, Loge et al. 1998). These studies have, however reported cut-off points from multidimensional fatigue questionnaires i.e. the fatigue a combination of the symptom itself and its manifestations. The frequency of “how often they felt tired or worn out” was given by 14% of men and 20% of women (Schwarz et al. 2003). Since the definition of fatigue and the methods used to assess fatigue in previous studies vary, the frequency, duration and severity of fatigue among elderly people in the general population is not well known, and reference values from Sweden are lacking. Clarifications of the differences between the symptom of fatigue among the general population and patients with COPD may lead to a better understanding of the patients’ situation.

There are many definitions of fatigue but no one is generally accepted (Ream et al. 1996, Tiesinga et al. 1996). The North American Nursing Diagnosis Association (NANDA) defines fatigue as “An overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work at usual level” (p. 75) (NANDA 2005). Fatigue is mostly described by its impact on functioning (Fisk et al. 1994, Glaus et al. 1996, Ream et al. 1996); “Fatigue reflects perceived impact on cognitive, physical and psychosocial functioning” (p.79) (Fisk et al. 1994). “Fatigue involved decreased physical performance, extreme unusual tiredness, weakness and an unusual need for rest, which was distinctly different for healthy persons”
(p.82) (Glaus et al. 1996). “Fatigue is a subjective, unpleasant symptom that incorporates total body feelings, ranging from tiredness to exhaustion, creating an unrelenting overall condition, which interferes with individuals’ ability to function to their normal capacity” (p.527) (Ream et al. 1996). Here, fatigue is defined as a subjective unpleasant, whole body experience that impact on patients’ functioning. From a nursing perspective, the focus is not only on the symptom of fatigue but also how it affects daily life (Dodd et al. 2001), which can be referred to as functional performance (Leidy 1994).

There are a number of questions in use to measure the symptom of fatigue. Specific questions about the frequency, duration and severity of fatigue (Fisk et al. 1994). The severity of fatigue has been measured using the Visual Analogue Scale for fatigue (VAS-F) (Lee et al. 1991). For patients with COPD, the severity of fatigue has been measured by questionnaires, which measure broader concepts. In the Bronchitis emphysema symptom checklist, the severity of fatigue is included as an item (Kinsman et al. 1983a). In a disease specific questionnaire, Chronic Respiratory Questionnaire (CRQ), fatigue is described in the form of different negative energy levels, tired and “worn out or sluggish” (Guyatt et al. 1987). Many of the multidimensional questionnaires of fatigue are a combination of the symptom of fatigue and the impact of fatigue and thus a dimension focusing on the symptom (Piper et al. 1989, Schwartz et al. 1993, Smets et al. 1995).

An integrated model of fatigue has been developed by Piper, Lindsey and Dodd (1987). The model permits a multiple disciplinary perspective, allowing definitions and theories about fatigue to be evaluated. In this model, subjective manifestations of fatigue include physical, emotional, behavioural and cognitive or mental experience. Physical manifestations include tired arms, legs, and eyes, whole-body tiredness, having no energy, feeling weary, list-less or worn out. Emotional manifestations are described as abnormal or unpleasant experiences and feelings of impatience, irritability, disinterest or lack of motivation. Behavioural manifestations involve, that it takes longer to do things, more efforts is required and certain activities are no longer undertaken. Cognitive or mental manifestations, includes problems with memory, concentration or the ability to think clearly. The model also includes objective manifestations of fatigue, physiological, biochemical, metabolic and behavioural indicators that can be measured objectively (Piper et al. 1987).
Functional status

Functional status is defined as functional capacity, functional performance, functional capacity utilization and functional reserve (Leidy 1994). Patients with COPD experience decreased functional status and have reduced levels of spontaneous physical activity compared with healthy controls (Sandland et al. 2005). In functional capacity for patients with COPD the muscle function plays a role. Decreased muscle function is related to a loss of muscle mass including diaphragm, respiratory and peripheral skeletal muscle (Engelen et al. 1994, Gosker et al. 2000, Troosters et al. 2005). There are conflicting results as to whether patients with COPD have lower handgrip strength as compared to healthy individuals (Engelen et al. 1994, Gosselink et al. 1996, Heijdra et al. 2003). Patients with normal FFM have reported normal handgrip strength (Heijdra et al. 2003) and patients with decreased FFM reported lower handgrip strength (Engelen et al. 1994). The patients who experience exertional dyspnoea are reported as markedly inactive as compared to healthy controls, the sitting and lying times are higher and movement intensity during walking is slower (Pitta et al. 2005). The walking distance during a six minutes interval has been found to be shorter for patients with COPD than for elderly controls (Peruzza et al. 2003). In order to avoid dyspnoea, the patients reduce their physical activity, which leads to muscle weakness and muscle fatigue during exercise (Mador et al. 2000, Saey et al. 2003). The most common strategy to improve functional capacity for patients with COPD is improving their walking capacity (Troosters et al. 2005).

Functional performance is influenced by functional capacity (Yeh et al. 2004) and reduced capacity limits performance of daily activities (Belza et al. 2001). Functional performance refers to activities that a person performs on day to day basis (Leidy 1994). The patients with COPD describe their functional performance or activities in terms of household activities (cleaning, meal preparation, lawn care), movement (carrying objects, walking up hills, climbing steps), family activities (caring for children, grandchildren and pets), social activities (getting together with others, conversation, playing cards), recreational activities (travelling, viewing live or videotaped musicals, watching certain television shows, reading, gardening, fishing) and pastimes (Guthrie et al. 2001, Leidy et al. 1996).

Several symptoms are reported to be associated with functional performance for patients with COPD. One study reported that fatigue, dyspnoea and depressed mood, including airflow obstruction accounted for 36% of the variance in functional performance (Kapella et al. 2005).
Several studies have reported that fatigue has a negative association with functional performance (Breslin et al. 1998, Kapella et al. 2006, Reishtein 2005). Few studies have examined how fatigue impacts on COPD patients’ functioning. In a qualitative study by Ream and Richardson (1997) patients have described that fatigue impacts on all activities of daily living and there was a gradual decline in their ability to carry out activities. Most of the patients were able to carry out only light housework and self-care and not able to participate in social and family activities. Insufficient energy has also been described to reduce feelings of being effective (Leidy et al. 1999). One study reported that patients with COPD experienced more fatigue, on general fatigue, physical and mental fatigue and reduction in activity and motivation, than did a normal adult population (Breslin et al. 1998). However, the study group was of a small sample size (n = 41).

In qualitative studies among healthy individuals, fatigue was described as acute, subjective, sometimes overwhelming but of a temporary state with physical, emotional, behavioural (Aaronson et al. 2003) and cognitive (Glaus et al. 1996) manifestations. In a general population group, fatigue has been reported to impact on functioning (Björnsson et al. 2004, LaChapelle et al. 1998). However, one study included a relatively small sample size (LaChapelle et al. 1998) and the other was from a relatively young population with a mean age of 49 years (Björnsson et al. 2004). Reference values from older populations and Swedish samples are lacking. Because of the high prevalence of fatigue in patients with COPD a more comprehensive assessment is essential for understanding its contribution to functioning as well as for its effective management.

There are a number of multidimensional questionnaires available that combine the symptom and the impact of the symptom (Table 1). The symptom of fatigue are represented in the Piper Fatigue Scale (PFS) (Piper et al. 1989) as timing of fatigue, in the Multidimensional Fatigue Inventory (MFI) (Smets et al. 1995), as general fatigue and in the Fatigue Assessment Instrument (FAI) (Schwartz et al. 1993), as global fatigue severity. The impact of fatigue is represented by dimensions of physical, cognitive and psychosocial functioning in the Fatigue Impact Scale (FIS) (Fisk et al. 1994), situation-specific fatigue and fatigue consequences in FAI (Schwartz et al. 1993), reduced activity, reduced motivation and mental fatigue in MFI (Smets et al. 1995) and by affective and sensory dimensions in the PFS (Piper et al. 1989).
The difference between MFI and PFS is that PFS includes emotional expressions that patients with COPD have described (Ream et al. 1997, Small et al. 1999). However, PFS has been tested on a small sample of patients with COPD and found that the patients had difficulties in assessing their fatigue on a visual analogue scale (VAS) (Small et al. 1999). The FAI also uses a VAS (Table 1). A questionnaire that assesses only the impact of fatigue is FIS, which also has a reference period of 30 days, indicating chronic fatigue (Piper 1993). In clinical practice, measurements that separate the symptom and the impact are preferable, as symptom questions can be used as screening questions. For patients with COPD, the FIS would seem to be a suitable questionnaire, as it only reflects only items of functional limitations in different dimensions, as described by the patients with COPD.

<table>
<thead>
<tr>
<th>dimensions</th>
<th>Reference period</th>
<th>Number of items</th>
<th>Scale</th>
</tr>
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<tbody>
<tr>
<td>FAI</td>
<td>Global fatigue severity, situation-specific fatigue, fatigue consequences, responsiveness to rest/sleep.</td>
<td>Two weeks</td>
<td>29</td>
</tr>
<tr>
<td>FIS</td>
<td>Physical, psychosocial, cognitive</td>
<td>30 days</td>
<td>40</td>
</tr>
<tr>
<td>MFI</td>
<td>General fatigue, physical fatigue, reduced activity, reduced motivation, mental fatigue</td>
<td>last few days</td>
<td>20</td>
</tr>
<tr>
<td>PFS</td>
<td>Temporal, intensity/severity, affective, sensory</td>
<td>now</td>
<td>40</td>
</tr>
</tbody>
</table>

FAI = Fatigue Assessment Instrument
FIS = Fatigue Impact Scale
MFI = Multidimensional Fatigue Inventory
PFS = Piper Fatigue Scale

General health perceptions
Patients with COPD have a substantial impairment in health perceptions (Mahler et al. 1995a, Peruzza et al. 2003, Spencer et al. 2001). Compared to a general population group, the patients had worse general health, on physical functioning, physical role function, bodily pain, general health, vitality, social functioning, emotional role function, and mental health, (Spencer et al. 2001). There are specific symptoms (e.g. dyspnoea and fatigue) and functions that are problematic for patients with COPD and that health questionnaires capture (Guyatt et
al. 1987, Jones 1995). In these, however, the functioning is only in relation to respiratory symptoms: such as dyspnoea, cough and sputum and physical activities that are limited by dyspnoea (Jones et al. 1992). That is, little attention has been paid to how fatigue limits COPD patients’ functioning and health.

Biological functioning, such as lung function has been shown to be of minor importance for health (Mahler et al. 1995b, Oga et al. 2004) but dyspnoea is reported to have a strong relation to health (Mahler et al. 1995a), although a recent study reported that health deteriorates with disease severity (Stahl et al. 2005). Functional capacity has been reported to influence health (Curtis et al. 1994, Jones 1995, Ketelaars et al. 1996). Recently it has been shown that biological functioning such as FEV$_1$ is not related to dyspnoea but to physical functioning and that physical functioning and dyspnoea are related to general health (Arnold et al. 2005). Fatigue is also reported to be associated with health (Belza et al. 2001, Yeh et al. 2004) but one of the studies used a subscale of a health questionnaire to evaluate fatigue (Yeh et al. 2004) and the other evaluated it only over the past week (Belza et al. 2001). However, it is unclear how different degrees of fatigue severity impact on health in patients with COPD.

**Characteristics of the individual and the environment**

Characteristics of the individual and the environment are not well described in patients with COPD. Women with COPD have reported more fatigue (lack of energy during the past week) than men in terms of intensity and frequency, but the women also had worse pulmonary function (Gift et al. 1999). In the general population contradictory results between fatigue and gender have been shown. In a Dutch working population, no association between fatigue and gender was seen (Bultmann et al. 2002) but in studies from Norway and Germany, women experienced more fatigue than men did (Loge et al. 1998, Schwarz et al. 2003). There are also conflicting results between fatigue and age, there were no associations in a study from the USA (Chen 1986) but in the study from Germany, fatigue increased with age (Schwarz et al. 2003). A Danish general population study reported that women scored higher on general fatigue and lower on reduced motivation than men did. Physical fatigue, reduced activity and reduced motivation increased with age (Watt et al. 2000).

There are limited data concerning the relation between functional status and gender in patients with COPD. In one study, women with COPD reported shorter walking distances compared to men (de Torres et al. 2005). The handgrip strength was reported not to differ between men
and women in patients with COPD nor between patients and control subjects (Heijdra et al. 2003). However, in that study, all the patients had near normal fat free mass index (FFMI) indicating normal muscle mass. Women have reported more functional limitations than men have, indicating that the functional performance may be different for men and women (Leidy et al. 1995).

There are contradictory results concerning gender and health. Women with COPD have reported worse health compared to men (Carrasco Garrido et al. 2006, de Torres et al. 2005) but in other studies, no interaction have been found between health and gender (Stahl et al. 2005, Vestbo et al. 2004). In patients with FEV₁ below 50% of predicted, there were no significant differences between men and women on health but women with an FEV₁ > 50% of predicted, had worse health compared with men (de Torres et al. 2006). There are differing results about the association between age and health. One study reported that there was no significant correlation between age and health (Ketelaars et al. 1996) but another study found that health deteriorates with age (Oga et al. 2004, Stahl et al. 2005). Physical health has been reported to have a relation to age (Carrasco Garrido et al. 2006).

Social isolation has been described by patients with severe COPD (Seamark et al. 2004) and social support from family, peers and health care professionals has been described as being important (Cicutt et al. 2004). Social support is reported to indirectly influence functioning (Graydon et al. 1995) and to be a motivator to perform disease management activities (Cicutt et al. 2004).

**Pulmonary rehabilitation**
Pulmonary rehabilitation is defined as a “multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy” (National Heart Lung and Blood Institute 2003). The goals of pulmonary rehabilitation are to reduce symptoms, increase physical and emotional participation in everyday activities and improve quality of life (Berry et al. 1999). There are ongoing discussions about which criteria are to be used for prescribing pulmonary rehabilitation. Earlier, patients with severe COPD were believed not to be candidates for exercise training but recently a study has shown that both patients with severe, moderate and mild COPD have reported improvements in functional capacity (Spruit et al. 2004). According to Spruit et al. (2004), pulmonary rehabilitation should be offered to patients who
after pharmacological therapy, continue to have symptoms of dyspnoea and fatigue. According to GOLD pulmonary rehabilitation should be offered to patients with an FEV$_1$ below 80% of predicted (Troosters et al. 2005). In Sweden, the national guidelines state that a multidisciplinary program should be taken into consideration when patients have multiple needs (Socialstyrelsen 2004). According to the Swedish national guidelines, after optimal pharmacological therapy, pulmonary rehabilitation should be offered at least to patients that have functional limitations of dyspnoea and fatigue, since these symptoms are experienced as the most severe.

The different components of pulmonary rehabilitations aim to improve the physical and psychological functioning of patients; interacting with the environment, enhancing knowledge of the disease and improving self-management. The rehabilitation programs are to be set up as individualized and multidisciplinary interventions (Lacasse et al. 2001). The components included in pulmonary rehabilitation vary from program to program but exercise training is the key component, with different combinations of educational sessions with a nurse specialist, occupational therapy, dietary interventions and psychosocial support. The duration and frequency of exercise training have not been adequately investigated but it is generally believed that longer programs yield more training effects. This is based on that 20 sessions compared to 10 sessions of pulmonary rehabilitation having shown greater improvements on health and seven weeks having shown more benefits than four weeks (Green et al. 2001). However, the outcomes were not on functioning. A recent statement from the ATS and ERS recommend a minimum of 20 sessions at least three times per week to achieve physiologic benefits (Nici et al. 2006).

Exercise training as a component in pulmonary rehabilitation improves functional capacity. In a meta analysis of 23 randomised controlled trials, the effect on six minutes’ walking distances (6MWD) was improved by 49 m (Lacasse et al. 2006). The minimal clinically important difference (MCID) has been estimated to be 54 m (Redelmeier et al. 1997). Exercise training with three sessions per week for 12 weeks or more exceeded the MCID (Bendstrup et al. 1997, Guell et al. 2000), while training twice a week for less than 12 weeks did not reach the MCID (Engström et al. 1999, Ringbaek et al. 2000). The effects of programmes that included occupational intervention, consisting of two lessons teaching techniques to overcome impairments in everyday tasks, reported improvements after 12 weeks’ intervention (Bendstrup et al. 1997). After 12 weeks of rehabilitation, including
occupational intervention with information about energy-saving techniques, at two sessions, there was no improvement in important functional aspects (Engström et al. 1999). When improvements were reported the occupational sessions consisted of everyday tasks listed by the patients (Bendstrup et al. 1997).

Several studies have evaluated the effects of health, including symptom and functioning, after pulmonary rehabilitation. A meta-analysis of 23 randomized controlled studies has been carried out by Lacasse et al. (2006). Eleven of these studies included outpatients’ rehabilitation, with sample sizes varying between 7 and 93 patients. The most used questionnaire was the CRQ (Bendstrup et al. 1997, Griffiths et al. 2000, Guell et al. 2000, Simpson et al. 1992, Troosters et al. 2000). The results showed that dyspnoea, fatigue and mastery domains of CRQ were both statistically significant and clinically relevant. In three of the outpatient rehabilitation programs included, the St George’s Respiratory questionnaire (SGRQ) was used (Engström et al. 1999, Griffiths et al. 2000, Ringbaek et al. 2000) and significant improvements were found on symptoms, activity and impact in one of the studies (Griffiths et al. 2000). Both the CRQ and the SGRQ measure dyspnoea relating to functional status and the CRQ also measures fatigue as severity. When improvements were found on the SGRQ, the patients attended the rehabilitation unit 3 half days per week for a period of 6 weeks (Griffiths et al. 2000).

In summary, pulmonary rehabilitation can improve the patients’ severity of fatigue and dyspnoea, walking distances, functioning in relation to dyspnoea, and health. However, despite fatigue being an important symptom for patients with COPD, it has not been evaluated in relation to functioning after pulmonary rehabilitation.
RATIONALE FOR THE THESIS

Functional performance is an important outcome for patients with COPD and is often associated with symptoms such as fatigue and dyspnoea. The relation between different degrees of fatigue severity, functional performance and health has not been adequately investigated. Pulmonary rehabilitation is a multidisciplinary treatment in the management of patients with COPD. It is well known that pulmonary rehabilitation improve the patients’ severity of fatigue and dyspnoea, functional capacity and health. Whether pulmonary rehabilitation can improve the patients’ functional limitations due to fatigue has not been investigated. There are many questionnaires measuring fatigue and the impact of fatigue. FIS is the only one that measures only the impact of fatigue e.g. functional limitations in daily living.

AIMS OF THE THESIS

The overall aim of the thesis was to describe fatigue, functional limitations due to fatigue and health among patients with COPD, compare patients with individuals from the general population, test if pulmonary rehabilitation can reduce fatigue and functional limitations due to fatigue, and improve health, as well as to validate the FIS among patients with COPD.

The specific aims were:

- to describe the frequency, duration and severity of fatigue among patients with COPD and the impact of perceived fatigue on cognitive, physical and psychosocial functioning in comparison with controls (I).
- to make a comparison between patients with COPD and individuals in a comparison group in terms of fatigue, functional limitations due to fatigue and health and also to assess the differences of functional limitations due to fatigue and health between patients experiencing no, moderate and severe fatigue (II).
- to test the effects of pulmonary rehabilitation on fatigue, functional status and general health in patients with COPD (III).
- to investigate reliability and validity of the FIS among patients with COPD, and study the effect of shortening the questionnaire (IV).
METHODS

This thesis consists of four clinical studies in patients with COPD (I-IV) which are based on three samples.

Participants

The participants in sample 1 (I) comprised 44 patients, 17 were men and 27 were women diagnosed as having COPD and registered between January 1997 and March 2000 at a pulmonary outpatient department in a central county council of Sweden. The inclusion criterion was 75 years of age, or younger. Patients registered as having asthma and/or cancer were excluded. To provide an equivalent group, two sex and aged matched individuals were randomly assigned for each patient with COPD from the regional population register of the same region as that of the patients. In total, 36 (81%) patients and 37 (42%) individuals from the general population answered the questionnaire.

The participants in sample 2 (II, IV) comprised 583 patients, 263 were men and 320 were women, diagnosed as having COPD, 75 years of age or younger and registered during 2002 at three outpatients departments from two university hospitals (n = 371 and n = 185) and one from a district hospital (n = 27) in Sweden. The questionnaires were mailed to the patients’ homes and returned from 345 (59%) patients. For testing the FIS, 49 of these patients were excluded (37 did not experience any problem with fatigue, three did not complete the questionnaires and 9 had six or more missing items) (IV). In study II, the participants comprised 212 patients from one of the university hospital and the district hospital and 212 individuals, of the same age and gender as the patients, randomly assigned from the regional population register of the same region as that of the patients. The questionnaires were answered by 151 (71%) patients and 95 (45%) individuals (II). There were no statistically significant differences between respondents and non respondents among the patients with regard to age and gender. The non respondents in the comparison group were older than the respondents ($p > 0.001$) and there were more men than women ($p = 0.01$) (II).
The participants in sample 3 (III) consisted of 30 patients, 13 were men and 17 were women, diagnosed as having COPD (BTS 1997) from an outpatient pulmonary department in a central county council of Sweden. The inclusion criteria were 75 years of age or younger, FEV$_1$ between 60% and 25% of predicted after bronchodilatation, a stable condition and COPD related symptoms that affect activities of daily living. The exclusion criteria were disabling or severe disease other than COPD, other disease causing impaired pulmonary function, pulmonary hypertension, COPD oxygen required, alpha 1-antitrypsin deficiency, cancer disease and untreated obstructive sleep apnoea syndrome. Thus, the analysed groups, on treatment-groups, consisted of 12 patients in the rehabilitation group and 14 patients in the control group (Figure 3).
Design
Two studies (I, II) had a descriptive comparative design in order to describe fatigue and the functional limitations due to fatigue (I, II) and health (II) in comparison to the general population.

A further study (III) was a prospective randomised clinical trial in which patients with COPD were randomly allocated either to a rehabilitation group that received pulmonary
rehabilitation for 12 weeks or to a control group that received usual care, without rehabilitation.

A final study (IV) was designed to investigate the reliability and validity of the FIS for use in patients with COPD, and the effect of shortening the questionnaire.

**Intervention with pulmonary rehabilitation (III)**
The pulmonary rehabilitation programme was multidisciplinary, comprising the following team members: a physiotherapist, dietician, occupational therapist and a nurse. Patients attended the physiotherapy unit two days per week for 12 weeks in groups of one to five. Each training session was approximately one hour long. The physiotherapy programme started with bicycle training for 10-15 minutes. The programme proceeded with exercises for muscle and strength training of biceps, latissimus dorsi and quadriceps and stand-ups, toe-raises, step-ups, pelvic-lifts and sit-ups in sessions of 10 exercises in three rounds per occasion. The patients’ efforts were followed with a Borg score rating from 0 (nothing at all) to 10 (very, very strong) (Borg 1982) and oxygen saturation (Nonin Onyx). If oxygen saturation decreased to a level below 90%, exercise was not increased. Whenever possible, the intensity of the programme was gradually increased. After one month, the patients received an individualised home training programme in addition to the physiotherapy session. This home training programme included written instructions for daily walks and muscle and strength training. A rubber band (Thera-Band) was used for upper extremity strength training.

The dietician educated the patients about the importance of adequate intake of energy and nutrients and also gave individual dietary advice. Patients with a BMI below 20 received additional nutritional supplementation (respifor 3x125 ml/day containing 635 kJ/100ml) and one patient with obesity (BMI > 30) received special nutritional advice. The patients were followed up three times (at weeks 2, 4 and 8) in connection with the physiotherapy sessions, each session lasting 30-60 minutes.

At baseline, the patient and the occupational therapist identified and discussed activities involving self-care, productivity and leisure that caused the patients difficulties according to the Canadian Occupational Performance Measure (COPM) (Law et al. 1998). The occupational therapist also educated the patients about energy saving techniques in relation to personal care, bedding, cooking, cleaning and laundry. The value of schedule a day and week,
in order to save energy was also discussed during the occupational sessions. The patients were followed up three times (at weeks 2, 4 and 8).

The nurse educated the patients about their disease, how to manage medications, exacerbations and gave self-care advice. Discussions regarding self-care advice were based on the patients expressing their own restrictions. Smokers were given non-smoking advice. The nurse sessions were conducted twice, at weeks 2 and 4. The whole team taught the patients breathing techniques.

The occupational therapist, dietician and nurse sessions were scheduled close in time to the physiotherapist sessions.

**Assessments**

*Biological function*

Pulmonary function, FEV\(_1\), was assessed at baseline and after 12 weeks using routine spirometry. Spirometry was performed using vitalograph spirometer (Buckingham, England) at the start of the study and a Vmax20c (Sensor medics, USA) after two years. Paired comparisons between FEV\(_1\), assessed with the Vitalograph and the Vmax20c did not show any statistically significant differences (n = 12). The spirometry was carried out 15 minutes after inhalation of 0.8 mg Sulbutamol or 2 mg Terbutaline, depending on patients’ use or, otherwise with 0.8 mg Salbutamol. Weight was measured with the patient in light clothing without shoes to the nearest 0.1kg (SECA 707, Ergo Nordic Sweden). Height was measured using a horizontal headboard with a wall-mounted metric (III).

*The symptoms of fatigue*

Fatigue was assessed with structured questions about frequency, duration and severity of fatigue (Fisk et al. 1994). The frequency of fatigue for the past 30 days was scored from 0 = not a problem, 1 = problems on 1 to 4 days, 2 = problems on 5 to 9 days, 3 = problems on 10 to 19 days, 4 = problems on 20 to 29 days and 5 = problems every day. The duration of fatigue was scored from 0 = no experience, 1 = less than 6 hours/day, 2 = 6-12 hours/day and 3 = 12-24 hours/day. The severity of fatigue was scored from 0 = not a problem, 1 = my least severe symptom, 2 = one of my less severe symptoms, 3 = one of my worst symptoms to 4 = my worst symptom (I - IV).
**Functional status**

Functional capacity was assessed by a 6MWD test with standardized instructions that the patient had to walk as far as possible for 6 minutes (ATS 2002). The patient walked back and forth in a 30 m corridor. Hand grip strength was measured with the Grippit instrument (AB Detektor, Sweden) (Nordenskiöld et al. 1993). The patient sits in a fixed test position and the dominant hand grips the handle for 10 seconds. The peak value out of two tests was taken as the value (Hammer et al. 2003) (II).

Functional limitations due to fatigue were assessed with FIS (Fisk et al. 1994). The FIS comprises 40 items and assesses functional limitations due to fatigue in the cognitive (10 items), physical (10 items) and psychosocial (20 items) dimensions (Appendix I). The patients were asked to rate the extent of the fatigue that had caused them problems during the past month in relation to exemplar statements. The items are scored from 0 = no problem, 1 = small problem, 2 = moderate problem, 3 = big problem to 4 = extreme problem. Higher scores indicate greater problems with functional limitations due to fatigue. The FIS has shown high internal consistency, with a Cronbach’s alpha for the total scale being 0.98 and > 0.87 for the subscales and has been found to discriminate between different groups of patients (Fisk et al. 1994). The FIS has not been used previously for patients with COPD. The Swedish version of the FIS (Flensner et al. 2002), was used in the studies (I - IV).

Changes in functional performance and satisfaction over time were assessed with COPM (Law et al. 1998). COPM is considered to be a reliable tool with regard to patients with COPD (Sewell et al. 2001). The patient identified difficulties in self-care, productivity and leisure and rated them separately, in terms of their current level of performance and satisfaction, scoring from 1 (not performed or dissatisfied) to 10 (performed extremely good or extremely satisfied). The scores are separately summed and divided by the number of difficulties (III).

**General health perceptions**

Health was assessed using SGRQ (III) (Jones et al. 1992) and the SF-36 (II, III) (Ware et al. 1993). The SGRQ comprises 76 items divided into three components: Symptoms (problems caused by specific respiratory symptoms), activity (restrictions of activity caused by dyspnoea) and impact (impact on everyday life caused by the disease). Scores are calculated with summed weights for the responses from each of the components and a total score,
ranging from 0 to 100. Lower scores indicate better health. The Swedish version of the SGRQ has been shown to be a valid and reliable tool for patients with COPD (Engström et al. 1998).

The SF-36 comprises eight health domains: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (6 items), vitality (4 items), social functioning (2 items), role-emotional (3 items) and mental health (5 items). The response alternatives vary from two (“yes” and “no”) to six (Likert type scale). The reference period is the last four weeks and higher scores indicate better health. The SF-36 has been tested extensively and has shown good psychometric properties (McHorney et al. 1994, McHorney et al. 1993, Ware et al. 1993). The Swedish version of SF-36 was used in this thesis (Sullivan et al. 1995).

The participants completed questions about age, gender, marital status, employment and support/no support from another person if they were ill (I - IV).

Statistics
The data are presented as frequencies (I, II, III) and percentages (I, II), arithmetic means and standard errors of the mean (I, II, III, IV). Differences between patients and controls /individuals in comparison groups were analysed using chi-square (I, III, IV), Mann-Whitney U-test (I, III, IV) and Student’s t-test for independent groups (I, III, IV) and Student’s t-test for dependant groups (IV). The level of statistical significance was set at p < 0.05.

Logistic and multiple regressions were used to control for age (II). As age had no effect, the data are presented as frequencies and percentage for ordinal data and means and standard errors of the mean for interval data. Multiple significances were adjusted using Holm’s sequential Bonferroni procedure (III, IV). One-way ANOVA variance followed by Tukey’s (equal variance assumed) or Tamhane’s (equal variance not assumed) post hoc tests was used for testing differences between three independent groups (III). The three independent groups consisted of patients with no fatigue, moderate (my least severe symptom and one of my less severe symptoms) and severe fatigue (one of my worst severe symptoms and my worst symptom) (III).

The Pearson product-moment correlations were used for item-item, item-total and test-retest correlations (IV). Cronbach’s alpha coefficient was estimated for internal consistency (I, IV).
Statistical analysis was performed with the software SPSS 9.0, 12.0 (I-IV). Mplus (Muthén et al. 2004) was used for the confirmatory factor analysis within the STREAMS environment (Gustafsson et al. 2001) (IV). Maximum Likelihood procedure with robust estimation (MLR) (West et al. 1995) was used, because the descriptive statistics suggested that some items did not approximate the normal distribution. Primarily the Root Mean Square Error of Approximation (RMSEA) was used which measures the amount of discrepancy between the model and the data, as is strongly recommended in evaluation of model fit (Browne et al. 1993). However, Comparative Fit Index (CFI) and the chi-square goodness-of-fit test, are also reported as model fit tests. A RMSEA value less than .08 indicates reasonable fit and a value of approximately .05 or less indicates a close fit of the model to the data (Browne et al. 1993) (IV).

**Ethical consideration**

These studies were performed in accordance with the declaration of Helsinki. The Medical Research Ethics Committee of Örebro (Registration no. 500:16 201/00) (I, III) and the Research Ethics Committee of Linköping University (Registration no. 02-417) (II, IV), Sweden approved the studies. All participants were given written (I, II, IV), or written and oral information (III) about the study and that participation was voluntary. Furthermore, they were informed that their participation was voluntary and could be withdrawn by them at any time. The return of the questionnaires was considered to represent consent to participate (II, III). The data have been confidentially handled and presented on a group basis.
RESULTS

Characteristics of the individual and the environment (I-IV)

The mean age of the patients with COPD ranged between 64 and 66 years and for individuals in the comparison groups, between 57 - 64 years in different studies (Table 2). In study II the patients were statistically significant older compared with individuals in the comparison group ($p < 0.001$). Individuals in the comparison groups were statistically significantly more often employed compared to patients with COPD ($p < 0.001$) (I, II). More than 80% of the participants had support from another person, and there were no statistically significant differences between patients with COPD and individuals in the comparison groups (I, II) (Table 2). Comparison between men and women in patients with COPD showed no statistically differences with regard to frequency, duration and severity of fatigue, functional limitations due to fatigue and health (II) (data not shown).

After randomisation, there were statistically significantly more women than men in the rehabilitation group (9 women and 4 men) compared to the control group (3 women and 10 men) ($p < 0.05$) (III). Comparisons between men and women in the whole sample (III) showed no statistically significant differences with regard to marital status, support from another person in the case of illness, $\text{FEV}_1$ % of predicted, BMI, frequency, duration or severity of fatigue, 6MWD, functional limitations due to fatigue and health (data not shown) except that the men had higher hand grip strength, $367 \text{ N (± 120)}$ compared with $231 \text{ N (± 59)}$ for the women ($p = 0.001$).

The mean age for the patients in study IV was 64 ($\pm 0.5$) years.

Biological function (III)

Comparison between the rehabilitation group and the control group at baseline showed that there were no statistically significant differences with regard to mean $\text{FEV}_1$ % of predicted (35.1 (2.2) and 32.3 (2.5)) or mean BMI (24.3 (1.1) and 25.0 (0.9)) respectively (III). Among the patients in the rehabilitation group, 8 out of 12 patients had an $\text{FEV}_1$ of < 40 % of predicted, representing severe COPD. In the control group, 11 out of 14 patients had severe COPD. In the rehabilitation group two patients had a BMI < 20.
The symptoms of fatigue (I-III)

Almost half of the patients with COPD had problems with fatigue every day and more than 44% of the patients reported that fatigue was one of their worst symptoms (I, II).

The patients with COPD reported statistically significant higher frequency, longer daily duration and greater severity of fatigue compared with individuals in the comparison groups ($p < 0.01$) (I, II) (Table 3).

At baseline, there were no statistically significant differences between the rehabilitation and control groups with regard to frequency, duration and severity of fatigue (III) (Table 3).

Functional status (I-III)

The patients with COPD reported a statistically significant greater limitations due to fatigue on physical and psychosocial functioning compared to individuals in the comparison group ($p < 0.001$) (I, II) (Table 4). The patients reported a statistically significant greater limitations due to fatigue on cognitive functioning compared to individuals in the comparison group ($p < 0.05$) (I) that was not confirmed in study II (Table 4). Patients with severe fatigue had significantly greater limitations on cognitive, physical and psychosocial functioning compared with patients reporting moderate fatigue ($p < 0.001$) (II) (Table 5).

At baseline, there were no statistically significant differences between the rehabilitation and the control groups for grip strength, 6MWD and functional limitations due to fatigue (III) (Table 4).
Table 2. Characteristics of the individuals, the environment and biological function (I-III)

<table>
<thead>
<tr>
<th>Study I COPD</th>
<th>Study I Comparison</th>
<th>p</th>
<th>Study II COPD</th>
<th>Study II Comparison</th>
<th>p</th>
<th>Study III Patients with COPD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 36</td>
<td>n = 37</td>
<td></td>
<td>n = 151</td>
<td>n = 95</td>
<td></td>
<td>n = 12</td>
<td>n = 14</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Men</td>
<td>17 (47)</td>
<td>14 (38)</td>
<td>77 (51)</td>
<td>38 (40)</td>
<td></td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Women</td>
<td>19 (53)</td>
<td>23 (62)</td>
<td>74 (49)</td>
<td>57 (60)</td>
<td></td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Married/co-habiting</td>
<td>22 (61)</td>
<td>24 (65)</td>
<td>105 (70)</td>
<td>76 (80)</td>
<td></td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Employment</td>
<td>3 (8)</td>
<td>16 (43)</td>
<td>28 (19)</td>
<td>63 (66)</td>
<td>***</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Support from another person</td>
<td>30 (83)</td>
<td>33 (89)</td>
<td>141 (93)</td>
<td>90 (95)</td>
<td></td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (0.9)</td>
<td>64 (1.0)</td>
<td>65 (0.6)</td>
<td>57 (1.0)</td>
<td>***</td>
<td>66 (1.8)</td>
<td>64 (1.7)</td>
</tr>
</tbody>
</table>

Chi-square test and Student’s t-test
* p < 0.05, *** p < 0.001.
BMI = Body Mass Index
FEV$_1$ = Forced expiratory volume produced in first second
SEM = Standard error of the mean
Table 3 Frequency, duration and severity of fatigue in patients with COPD (I-III) and individuals in comparison groups (I-II).

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>n = 36</td>
<td>n = 151</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Frequency:</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Not a problem</td>
<td>7 (19.4)</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>15 (40.5)</td>
<td>28 (29)</td>
</tr>
<tr>
<td>1-4 days</td>
<td>4 (11.1)</td>
<td>19 (12)</td>
</tr>
<tr>
<td></td>
<td>8 (21.9)</td>
<td>21 (22)</td>
</tr>
<tr>
<td>5-9 days</td>
<td>2 (5.6)</td>
<td>17 (11)</td>
</tr>
<tr>
<td></td>
<td>6 (16.2)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>10-19 days</td>
<td>4 (11.1)</td>
<td>16 (11)</td>
</tr>
<tr>
<td></td>
<td>1 (2.7)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>20-29 days</td>
<td>2 (5.6)</td>
<td>10 (7)</td>
</tr>
<tr>
<td></td>
<td>2 (5.4)</td>
<td>5 (5)</td>
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<tr>
<td>Every day</td>
<td>17 (47.2)</td>
<td>73 (48)</td>
</tr>
<tr>
<td></td>
<td>5 (13.5)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Duration:</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>No experience</td>
<td>6 (16.7)</td>
<td>12 (8)</td>
</tr>
<tr>
<td></td>
<td>16 (43.2)</td>
<td>26 (27)</td>
</tr>
<tr>
<td>&lt; 6 hours</td>
<td>11 (30.6)</td>
<td>52 (34)</td>
</tr>
<tr>
<td></td>
<td>14 (37.8)</td>
<td>43 (45)</td>
</tr>
<tr>
<td>6-12 hours</td>
<td>12 (33.3)</td>
<td>37 (24)</td>
</tr>
<tr>
<td></td>
<td>6 (16.2)</td>
<td>17 (18)</td>
</tr>
<tr>
<td>12-24 hours</td>
<td>7 (19.4)</td>
<td>46 (31)</td>
</tr>
<tr>
<td></td>
<td>1 (2.7)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Severity:</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>Not a problem</td>
<td>9 (25)</td>
<td>18 (12)</td>
</tr>
<tr>
<td></td>
<td>19 (51.4)</td>
<td>39 (42)</td>
</tr>
<tr>
<td>One of my least</td>
<td>3 (8.3)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>severe symptoms</td>
<td>3 (8.1)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>One of my less</td>
<td>8 (22.2)</td>
<td>42 (28)</td>
</tr>
<tr>
<td>severe symptoms</td>
<td>11 (29.7)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>One of my worst</td>
<td>9 (25)</td>
<td>57 (38)</td>
</tr>
<tr>
<td>problems</td>
<td>4 (10.8)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>My worst problem</td>
<td>7 (19.4)</td>
<td>19 (13)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

Mann-Whitney U-test

** p < 0.01, *** p < 0.001, a) = p-value controlled for age.
Table 4. Functional capacity and functional limitations due to fatigue in patients with COPD (I-III) and individuals in comparison groups (I, II)

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COPD</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>n = 36</td>
<td>n = 139</td>
</tr>
<tr>
<td></td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
</tr>
<tr>
<td></td>
<td>Comparison p</td>
<td>p a)</td>
</tr>
<tr>
<td>n = 37</td>
<td>mean (SEM)</td>
<td>n = 67</td>
</tr>
<tr>
<td></td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
</tr>
</tbody>
</table>

**Functional capacity:**

- **Grip strength (N)**
  - Study I: 261.1 (24.3)
  - Study II: 331.5 (35.2)
  - Study III: 261.1 (24.3) vs 331.5 (35.2)

- **6MWD (m)**
  - Study I: 312.6 (23.9)
  - Study II: 360.3 (22.6)
  - Study III: 312.6 (23.9) vs 360.3 (22.6)

**Functional limitation due to fatigue:**

- **FIS (max score)**
  - Cognitive (40): 9.5 (1.5) vs 5.7 (1.1)
  - Physical (40): 19.2 (2.0) vs 6.8 (1.5)
  - Psychosocial (80): 30.9 (3.5) vs 10.2 (2.3)
  - Total (160): 59.6 (6.6) vs 22.7 (4.7)

* Student's t-test for independent groups
  * p < 0.05, *** p < 0.001. a) p controlled for age
  N = Newton
  6MWD = Six minutes’ walking distance
  FIS = Fatigue Impact Scale
Table 5. Comparison of functional limitations due to fatigue between patients with COPD experiencing moderate or severe fatigue (II)

<table>
<thead>
<tr>
<th></th>
<th>Moderate fatigue (n = 53) mean (SEM)</th>
<th>Severe fatigue (n = 76) mean (SEM)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIS (max score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive (40)</td>
<td>8.7 (0.9)</td>
<td>18.2 (1.0)</td>
<td>***</td>
</tr>
<tr>
<td>Physical (40)</td>
<td>18.0 (1.1)</td>
<td>27.8 (0.8)</td>
<td>***</td>
</tr>
<tr>
<td>Psychosocial (80)</td>
<td>26.4 (2.2)</td>
<td>46.5 (1.6)</td>
<td>***</td>
</tr>
<tr>
<td>Total (160)</td>
<td>53.1 (3.9)</td>
<td>92.5 (3.1)</td>
<td>***</td>
</tr>
</tbody>
</table>

Student’s t-test for independent groups: *** p < 0.001
SEM = Standard error of the mean
FIS = Fatigue Impact Scale

General health perceptions (II - III)

The multiple regression analysis showed that the patients with COPD had significantly worse health in all domains compared with individuals in the comparison group, controlled for age (p < 0.01) (II) (Table 6). The patients who reported severe fatigue had significantly worse health compared to patients reporting moderate fatigue (II) (Table 7).

At baseline there were no statistically significant differences between the rehabilitation group and the control group with regard to perception of health (III) (Table 6).

Effects of pulmonary rehabilitation (III)

At the 12 weeks’ follow up, fatigue, functional capacity, functional limitations due to fatigue and health in patients randomized to the rehabilitation group were not statistically significantly different compared with patients in the control group (data not shown). At the 12 weeks’ follow up, the patients within the rehabilitation group reported statistically significant improvements in six minutes’ walking distances (p = 0.02) (Table 8), performance (p = 0.002) and satisfaction (p = < 0.001) in their own selected activities compared with baseline (Table 9). The mean changes in functional capacity, functional limitations due to fatigue and health (baseline – 12 weeks follow up) within the rehabilitation group were not statistically significant compared with the mean changes within the control group (Table 8).
Table 6. Health perceptions in patients with COPD (II, III) and individuals in a comparison group (III)

<table>
<thead>
<tr>
<th>SF-36 domains (max score)</th>
<th>Study II COPD n =151 mean (SEM)</th>
<th>Study III Patients with COPD Rehabilitation n = 12 mean (SEM)</th>
<th>Study III Control n =14 mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning (100)</td>
<td>38.3 (2.2)</td>
<td>31.4 (5.3)</td>
<td>49.2 (5.5)</td>
</tr>
<tr>
<td>Role, physical (100)</td>
<td>24.9 (3.1)</td>
<td>9.1 (5.1)</td>
<td>36.1 (11.7)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>56.9 (2.4)</td>
<td>47.0 (5.5)</td>
<td>63.6 (8.7)</td>
</tr>
<tr>
<td>General health (100)</td>
<td>30.0 (1.6)</td>
<td>26.5 (4.1)</td>
<td>31.1 (4.8)</td>
</tr>
<tr>
<td>Vitality (100)</td>
<td>37.9 (2.1)</td>
<td>45.1 (6.2)</td>
<td>39.3 (5.3)</td>
</tr>
<tr>
<td>Social functioning (100)</td>
<td>58.1 (2.3)</td>
<td>63.6 (9.4)</td>
<td>58.3 (8.0)</td>
</tr>
<tr>
<td>Role, emotional (100)</td>
<td>44.5 (3.8)</td>
<td>60.6 (14.8)</td>
<td>66.7 (8.2)</td>
</tr>
<tr>
<td>Mental health (100)</td>
<td>63.0 (1.8)</td>
<td>70.1 (6.7)</td>
<td>65.3 (7.8)</td>
</tr>
</tbody>
</table>

One way ANOVA with Tamhane’s and Tukey’s post hoc tests as appropriate.

Student’s t-test for independent groups, ** p < 0.01 *** p < 0.001
a) p - value controlled for age

Table 7. Health perceptions in patients with COPD experiencing no, moderate or severe fatigue (II)

<table>
<thead>
<tr>
<th>SF-36 domains (max score)</th>
<th>No fatigue (n = 18) mean (SEM)</th>
<th>Moderate fatigue (n = 53) mean (SEM)</th>
<th>Severe fatigue (n = 76) mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning (100)</td>
<td>54.5 (7.3)</td>
<td>44.6 (3.1)</td>
<td>30.4 (2.9)</td>
</tr>
<tr>
<td>Role, physical (100)</td>
<td>66.7 (9.9)</td>
<td>28.0 (5.5)</td>
<td>11.3 (2.6)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>81.2 (5.6)</td>
<td>61.8 (3.5)</td>
<td>47.7 (3.6)</td>
</tr>
<tr>
<td>General health (100)</td>
<td>43.6 (6.2)</td>
<td>33.6 (2.5)</td>
<td>23.8 (1.9)</td>
</tr>
<tr>
<td>Vitality (100)</td>
<td>71.4 (5.0)</td>
<td>43.5 (2.6)</td>
<td>24.7 (2.3)</td>
</tr>
<tr>
<td>Social functioning (100)</td>
<td>86.1 (5.6)</td>
<td>66.0 (3.0)</td>
<td>44.7 (3.1)</td>
</tr>
<tr>
<td>Role, emotional (100)</td>
<td>83.3 (8.2)</td>
<td>56.7 (6.2)</td>
<td>44.1 (4.7)</td>
</tr>
<tr>
<td>Mental health (100)</td>
<td>82.4 (4.6)</td>
<td>71.1 (2.6)</td>
<td>52.2 (2.3)</td>
</tr>
</tbody>
</table>

One way ANOVA with Tamhane’s and Tukey’s post hoc tests as appropriate.

* p < 0.05, ** p < 0.01, *** P < 0.001
a) p between groups of no and moderate fatigue.
b) p between groups of moderate and severe fatigue.
c) p between groups of no and severe fatigue.
Table 8. Mean changes (SEM) (baseline - 12 weeks) in functional capacity, functional limitations due to fatigue and health within the rehabilitation and control groups (III). The mean changes within the rehabilitation group were not statistically significant compared with the mean changes within the control group.

<table>
<thead>
<tr>
<th></th>
<th>Rehabilitation group mean (SEM)</th>
<th>Control group mean (SEM)</th>
<th>p mean change within group</th>
<th>p mean change within group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip strength (Newton)</td>
<td>15.5 (10.7)</td>
<td>5.6 (13.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>40.6 (8.2)</td>
<td>*</td>
<td>16.5 (12.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Functional limitations due to fatigue</strong> FIS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>- 0.08 (2.0)</td>
<td>- 0.1 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>3.2 (1.9)</td>
<td>2.1 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial</td>
<td>4.2 (4.1)</td>
<td>- 0.1 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.3 (7.6)</td>
<td>1.9 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGRQ score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>10.6 (6.4)</td>
<td>- 0.5 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>2.5 (3.8)</td>
<td>2.7 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact</td>
<td>9.7 (4.5)</td>
<td>3.4 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7.6 (3.1)</td>
<td>2.6 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>- 10.5 (4.9)</td>
<td>1.1 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role physical</td>
<td>- 32.5 (13.5)</td>
<td>- 5.6 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>- 8.8 (6.9)</td>
<td>6.5 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>- 8.4 (5.3)</td>
<td>- 4.7 (2.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>- 7.3 (7.8)</td>
<td>- 8.2 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>- 2.5 (10.5)</td>
<td>- 6.2 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role Emotional</td>
<td>- 16.7 (12.4)</td>
<td>0.0 (14.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>- 4.9 (7.6)</td>
<td>- 4.0 (7.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Paired *t*-test for mean changes within group and unpaired *t*-test for differences between groups

* p < 0.05 for mean changes within groups, adjusted using Holm’s sequential Bonferroni procedure

SGRQ = St George’s Hospital Respiratory Questionnaire
SF-36 = Medical Outcomes Survey Short Form 36
FIS = Fatigue Impact Scale
6MWD = Six minutes' walking distance
SEM = Standard error of the mean
Table 9. Canadian occupational performance measure at baseline and after 12 weeks of pulmonary rehabilitation in patients with COPD (III)

<table>
<thead>
<tr>
<th>COPM</th>
<th>Rehabilitation group (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Performance</td>
<td>4.8 (0.6)</td>
<td>6.0 (0.5)</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>4.8 (0.6)</td>
<td>6.0 (0.6)</td>
</tr>
</tbody>
</table>

Paired t-test ** p < 0.01, *** P< 0.001
SEM = Standard error of the mean

Validity and reliability of the FIS (IV)

Construct validity of the FIS was initially investigated using Confirmatory Factor Analysis (CFA) on the three-factor model proposed by Fisk et al. (1994). The fit indices for the model, $\chi^2 (737, N = 296) = 2333.24$, $p<.00$ CFI = 0.82 and RMSEA = .086, showed that the fit of the model was not acceptable. Further analysis did not result in an acceptable fit.

In order to apply a theory on the empirically developed FIS, the Pipers’s theoretical framework of subjective manifestations of fatigue was tested, including behavioural, physical, emotional and cognitive dimensions (Piper 1993). The items were organised into four dimensions, behavioural (Beh), physical (Phys), emotional (Emo) and cognitive (Cog). Several alternative models were tested. During the procedure 15 items were reduced. The reduction of the items was based on theory, modification indices and factor loadings. Five items from the original cognitive dimension, seven item from the original psychosocial dimension and three items from the physical dimension were removed. After item reduction the fit indices of the model, $\chi^2 (269, N = 296) = 624.00$, $p<.00$ CFI = 0.92 and RMSEA = .067, indicated that the model has an acceptable fit (Model B, Table 10). The result also demonstrated a relatively strong interrelation of the four factors (ranging from 0.65 to 0.94). The strong relations between the factors indicates an underlying commonality (Snow et al. 1996), and is a reason to investigate a model with a hypothesized underlying factor.

A higher order model including one latent factor (Beh) at the apex was examined. The fit indices for this model were acceptable but poorer than for the four-factor model $\chi^2 (271, N = 296) = 727.13$, $p<.00$, CFI = 0.90 and RMSEA = .075 (Model C, Table 10). The
standardized factor loading of the specific Beh factor and the general factor was perfect and a reason to use this model for further modelling.

A nested-factor model (Model D, Figure 4) was investigated and tested. It was assumed that all items consist of behavioural components, since all the FIS items reflect functional limitations due to fatigue. A general Beh-factor was specified that was related to all 25 items and Cog, Emo and Phys factor were related to items of each specific dimension. Fit indices for this model showed a better fit $\chi^2 (256, N = 296) = 569.77, p<.00$ CFI = 0.93 and RMSEA = .064. Modification indices showed a relation between Cog and Emo and a covariance (r = 0.72) was included in the model. The model fit was further improved $\chi^2 (255, N = 296) = 482.49, p<.00$, CFI = 0.95 and RMSEA=.055 (Model D, Table 10). The standardized factor loading (Table 11) showed that the items were related to the general Beh factor and 19 of the 25 items also were related to the one of the specific factors.

Table 10. Summary of Goodness of Fit for Confirmatory Factor Analysis Models

<table>
<thead>
<tr>
<th>Model</th>
<th>$\chi^2$</th>
<th>df</th>
<th>CFI</th>
<th>RMSEA</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2333.24</td>
<td>737</td>
<td>0.82</td>
<td>.086</td>
<td>Original model of FIS</td>
</tr>
<tr>
<td>B</td>
<td>624.00</td>
<td>269</td>
<td>0.92</td>
<td>.067</td>
<td>Four-factor model</td>
</tr>
<tr>
<td>C</td>
<td>727.13</td>
<td>271</td>
<td>0.90</td>
<td>.075</td>
<td>Higher-order model</td>
</tr>
<tr>
<td>D</td>
<td>482.49</td>
<td>255</td>
<td>0.95</td>
<td>.055</td>
<td>Nested-factor model</td>
</tr>
</tbody>
</table>

CFI = Comparative Fit Index, RMSEA = Root Mean Square Error of Approximation.
Table 11. Standardised factor loadings from the nested-factor model

<table>
<thead>
<tr>
<th>Manifest factors</th>
<th>Physical</th>
<th>Emotional</th>
<th>Cognitive</th>
<th>Behavioural</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS3</td>
<td>.19</td>
<td></td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>PH13</td>
<td>.36</td>
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<td>PH17</td>
<td>.48</td>
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<td>.72</td>
</tr>
<tr>
<td>PH23</td>
<td>.12</td>
<td></td>
<td></td>
<td>.79</td>
</tr>
<tr>
<td>PH31</td>
<td>.30</td>
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</tr>
<tr>
<td>PH37</td>
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<tr>
<td>PH38</td>
<td>.22</td>
<td></td>
<td></td>
<td>.74</td>
</tr>
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<td>PS4</td>
<td></td>
<td>.31</td>
<td></td>
<td>.52</td>
</tr>
<tr>
<td>PS27</td>
<td></td>
<td>.33</td>
<td></td>
<td>.74</td>
</tr>
<tr>
<td>PH32</td>
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<td>.43</td>
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<td>.56</td>
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<td>PS33</td>
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<td>.50</td>
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<td>.59</td>
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<td>PS39</td>
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<td>.42</td>
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<td>PS40</td>
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<td>CO5</td>
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<td>CO11</td>
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<tr>
<td>CO18</td>
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<td>PS25</td>
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<td>.19</td>
<td>.79</td>
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<td>CO30</td>
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<td>CO35</td>
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<td>PS2</td>
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<td>.76</td>
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<td>.82</td>
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<td>PS16</td>
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<td>.80</td>
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<td>PS22</td>
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<td>.73</td>
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<td>PS29</td>
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<td></td>
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<td>.52</td>
</tr>
</tbody>
</table>

Item from the original Fatigue Impact Scale, PH= physical item, PS= Psychosocial item, CO= Cognitive
Figure 4. The nested-factor model (Model D)
Items from the original Fatigue Impact Scale, PH=Physical item, PS=Psychosocial item,
Correlation coefficients between item-item of the original FIS ranged from 0.32 to 0.80 and between item-total score from 0.60 to 0.80. The correlation coefficients between item-item for FIS-25 ranged from 0.31 to 0.75 and between item-total from 0.52 to 0.79. Cronbach’s alpha coefficient for the total scale for the FIS was 0.98, for the cognitive subscale 0.95, the physical subscale 0.93 and the psychosocial subscale 0.96. In study I, the Cronbach’s alpha coefficient for the total scale and the subscales were > 0.90. For FIS-25, the Cronbach’s alpha coefficient for the total scale was 0.96, for the Cognitive dimension 0.90, the physical dimension 0.93 and the Emotional dimension 0.89.

The sensitivity of the original FIS and the FIS-25 was evaluated with comparison between patients with different durations of fatigue. There were significantly higher scores on each item of the original FIS from patients who reported fatigue six hours a day or more (n = 181) compared to patients who reported fatigue less than six hours a day (p < 0.001). Test-retest correlations for FIS ranged between 0.70 and 0.85 for the items and 0.94 for the total scale score. Equal test-retest correlations were seen in FIS-25.
DISCUSSION
Half of the patients reported fatigue as a severe symptom. Patients with severe fatigue had more functional limitations due to fatigue and worse health as compared to patients with moderate fatigue. Although fatigue was an expected symptom, the patients with COPD experienced a higher frequency, longer daily duration and greater severity of fatigue than individuals from the general population did. After a 12 week pulmonary rehabilitation programme, there were no statistically significant differences between the patients randomised to the rehabilitation group and those in the control group. The patients within the rehabilitation group improved walking distances, performance and satisfaction with regard to their own selected activities, as compared to baseline. No effects were found on fatigue or functional limitations due to fatigue. The validation of the FIS resulted in a reduction of 15 items and provided support for Pipers’ theoretical framework of subjective manifestations of fatigue, including one general behavioural and three specific, physical, emotional and cognitive dimensions. The shorter version of FIS’s internal consistency, sensitivity and stability are satisfactory.

The symptoms of fatigue
In this thesis, fatigue was found to be a significant problem among patients with COPD with no differences between men and women. Fatigue was also related to the patients’ functional status and perception of health. Based on these results, fatigue is an important symptom requiring assessment and management.

Despite, the high prevalence of fatigue among patients with COPD, fatigue is reported to be difficult to separate from other symptoms associated with it. Dyspnoea is reported as a significant predictor of fatigue (Gift et al. 1999) and shows the highest correlation with fatigue among variables such as pulmonary function, depressed mood, anxious mood and sleep quality (Kapella et al. 2006). It is suggested that the symptoms are experienced simultaneously (Lenz et al. 1997). However, the nature of fatigue and dyspnoea in patients with COPD are different; fatigue is experienced with no relation to activity or exertion while dyspnoea is often experienced upon exertion. A better understanding of the underlying mechanism of fatigue is needed. In this thesis, dyspnoea was not assessed, except as a symptom dimension included in the SGRQ (III). A limitation of this thesis is that dyspnoea was not measured in terms of frequency and severity. However, longitudinal studies of the occurrence of and relation between fatigue and dyspnoea along the trajectory of the disease
are needed, as is knowledge of the separate effects of these two symptoms on functional performance.

Fatigue is a symptom that is rarely assessed by health care professionals (Detmar et al. 2001, Tiesinga et al. 2002). Detmar et al. (2001) reported that when patients undergoing palliative treatment initiated discussions about fatigue, the professionals tended to ignore the symptom because of lack of knowledge to assess it. The mechanisms or aetiology of fatigue are at present poorly understood. If treatment is to be implemented, adequate assessment of this symptom and a better understanding of its constitution is necessarily.

**Functional status**
The patients with COPD had more limitations due to fatigue on physical and psychosocial functioning as compared to the comparison group from the general population. There were no differences on cognitive functioning in comparison with the general population. This indicates that the impact of fatigue on cognitive function is less than its impact on physical and psychosocial functioning. These results demonstrate that the impact of fatigue on physical and psychosocial functioning led to the major functional limitations in patients with COPD. The impact of fatigue seems to be as high as in patients multiple sclerosis (Fisk et al. 1994, Mathiowetz 2003) and higher than in patients with brain injury (LaChapelle et al. 1998). Patients experiencing severe fatigue had significantly more limitations due to fatigue on cognitive, physical and psychosocial functioning in comparison with patient experiencing moderate fatigue. This could indicate that the cognitive dimension is more affected when fatigue is severe. Knowledge about when the cognitive impact of fatigue occurs in the trajectory of the disease is required. Different interventions are probably needed when the patients experience different severities of fatigue.

**General health perceptions**
Patients experiencing moderate fatigue reported better general health and mental health compared with patients’ experiencing severe fatigue. The relation between fatigue and health has not been adequately investigated, since general health represents a more overall evaluation of how the patients experience their health (Ferrans et al. 2005). Health questionnaires used in research among patients with COPD include items and dimensions that measure both symptoms and functional status and it is the summated scores that actually represent health (Jones et al. 1992). Taking this into consideration, only one study has to our
knowledge, reported fatigue to be correlated with general health (Breslin et al. 1998). The SF-36 summary component scores physical component summary and mental component summary have, in Swedish settings, indicated that the components are not independent. Furthermore the Swedish normal population score differs from scores obtained from the United States (Taft et al. 2001), which is why these components’ scores were not used in this thesis.

The patients with COPD reported significantly worse general health and mental health compared with individuals from the general population. The scores for general health and mental health from the general population in this study represent a Swedish normal population. When comparing the scores from the Swedish norm data base of individuals between 55 and 64 years of age with the individuals in this study, no significant differences were seen (Sullivan et al. 1994). To our knowledge, this is the first report on comparisons between patients with COPD and a general population, operationalised as general health and mental health on SF-36.

According to the conceptual model for health related quality of life (Ferrans et al. 2005), it is hypothesized that biological functioning influences symptom, which in turn influences functional status, which in its turn influences general health perception and quality of life (Figure 1). Wilson and Cleary’s model (Wilson et al. 1995) has recently been tested from a symptom of dyspnoea perspective (Arnold et al. 2005). These authors did not found any relation between pulmonary function and dyspnoea. However, this is consistent with other studies (Singh et al. 2001, Wijnhoven et al. 2001). Dyspnoea was directly correlated to both physical functioning and general health (Arnold et al. 2005). Although, these studies show that fatigue is related to both functional status and general health (II), the model could not be tested completely due to small sample size from biological function components (III) and quality of life has not been in focus in this thesis. Further studies with careful operationalization of the constructs and inclusion of relevant variables in each component need to be carried out. In order to evaluate the causal relationships among suggested components in the model, prospective, longitudinal designs are required. Such evaluations would also be of value because perception of health and quality of life are dynamic concepts that change over time (Cosby et al. 2000).
Effects of pulmonary rehabilitation

Pulmonary rehabilitation was tested with the purpose of improving fatigue, functional status and health. No statistically significant differences in mean changes were seen between the rehabilitation group and the control groups with regard to fatigue. Improvements in fatigue have previously been reported in the fatigue domain when using CRQ (Lacasse et al. 2006). The fatigue domain in CRQ consists of four questions on a 7-point scale and the summated scores represent fatigue. In this study frequency, duration and severity of fatigue were separate scales and therefore less sensitive to change than the CRQ.

In the evaluation of the effects of pulmonary rehabilitation on symptoms and functioning, most studies focus on dyspnoea and its impact of dyspnoea although fatigue is recognised as one of the cardinal symptoms in limiting the patients’ functional capacity (Nici et al. 2006). In a comprehensive approach to measuring the outcome on symptoms and functioning both dyspnoea and fatigue needs to be assessed. There is a need to develop a questionnaire that includes both these symptoms and functioning for use in patients with COPD. Nevertheless, different approaches for the management of fatigue necessitate further studies.

Improving functional performance is a goal in the care of patients with COPD, particularly in pulmonary rehabilitation (ACCP/AACVPR 1997, Pauwels et al. 2001). In this study, patients in the rehabilitation group improved functional capacity after 12 weeks of pulmonary rehabilitation, but this was not confirmed when the changes were compared with changes within the control group. Functional capacity has been found to be related to functional performance (Leidy 1995) and a key to a successful rehabilitation (Lacasse et al. 1997). However, as the goal is to improve the functional performance, measuring the functional performance directly is more relevant. For that purpose, the FIS-25 could be a useful questionnaire as it reflects limitations in functional performance related to fatigue, one of the worst symptoms that the patients perceive. The FIS was used to evaluate the effects of pulmonary rehabilitation. Although the power was low, and the sample size was small, the results indicate that there are positive effects of the rehabilitation. When the patients in the rehabilitation group expressed their own wishes to improve some activities of daily living, performance and satisfaction were improved. This has also been reported by others (Bendstrup et al. 1997, Sewell et al. 2005). In programmes with the purpose of individualizing pulmonary rehabilitation, the COPM could be a useful tool for improving the patients’ functional performance. Further research, with larger sample sizes, is needed in
order to evaluate the effects of individualized pulmonary rehabilitation on functional performance.

The length and the content, in the form of the frequency of the different sessions, of the rehabilitation programme might not have been sufficient for a chronic disease. Firstly, the 12 weeks’ follow-up of this study is a relatively short time frame. Secondly, the frequency of the sessions was twice for the nurse and three times for the occupational therapist and the dietician, which might be too few sessions. On the other hand, education that included information and treatment about COPD and symptom awareness, given as two 2-hour group sessions in combination with one or two 40 minute individual sessions, has reported positive effects (Gallefoss et al. 1999). In that study, the patients in the intervention group reduced the need for rescue medication, which increased the use of medications. A review study has, however, concluded that there were no effects of self-management education on hospital admissions, emergency room visits, days lost from work and lung function and inconclusive results were found on symptoms and on disease specific questionnaires (Monninkhof et al. 2006).

In rehabilitation programmes, such as in this study, behavioural changes are to be made in terms of using energy-saving techniques, improving dietary habits, learning how to breathe, disease acceptance, taking care of exacerbations and maintaining exercise. Behavioural changes probably require a series of stages in order to improve health perception (Bourbeau et al. 2004). A more planned intervention, with sessions concerning both knowledge and skills is needed (Bourbeau et al. 2004). Perhaps more specific performance training, with transformation of knowledge and skills acquired into the home setting, would be a better way of bringing about a change in behaviour. In this study, the extent of the intervention by the nurse, occupational therapist and dieticians might not have been enough. It is important to conduct studies, of sufficient sample size, evaluating the effects of education on self-management strategies and behavioural change in patients with COPD.

In this study, there were 8 patients with severe COPD included in the rehabilitation group. These patients may have adapted to a sedentary life style and low functional status over a long period of time. Improvements of fatigue perception and functional limitations due to fatigue may require long term intervention and follow-up.
Validation of the FIS

When validating the FIS, a shorter version, comprising 25 items, was developed. Although the FIS has not been shown to be difficult to complete (I), a shorter version has been sought after (Mathiowetz 2003). FIS was developed for patients with multiple sclerosis (Fisk et al. 1994) but it is now used in a variety of medical conditions (Björnsson et al. 2004, Martinez-Martin et al. 2006, On et al. 2006). The initial validation was from patients with multiple sclerosis, with a mean age of 38 years (Fisk et al. 2002). The mean age of individuals included in this thesis varies between 64 and 66 years. In shortening the questionnaire, many of the items that were omitted refer to situations that might be less applicable to older people, such as providing financial support and care for the family.

The homogeneity of the original FIS, as assessed with Cronbach’s alpha in these studies was > 0.90 (I, II) indicating that there might be some overlapping items (Streiner et al. 2003). A high Cronbach’s alpha (> 0.90) and high item-item correlations (r ≥ 0.70) has also been reported by others (Fisk et al. 1994, Flensner et al. 2005). The Cronbach’s alpha for the FIS-25 remains high, but has decreased. Thus, the FIS-25 ought to be more relevant for patients with COPD and not tiring in itself.

The model by Fisk et al. (1994) did not result in an acceptable fit. In order to apply theory on the Fisk et al’s model, the Piper’s theoretical framework of fatigue (Piper 1993) including behavioural, physical, emotional and cognitive manifestations was used in the validation of the FIS. This resulted in support for the dimensions of Piper’s manifestation of fatigue. In a recent review of self reported instruments for assessment of fatigue, it was proposed that a definition of fatigue encompasses physical, cognitive and emotional dimensions (Mota et al. 2006). However, all remaining items in this study consisted of a behavioural component. Recently it has been proposed that all the items of FIS are related to behavioural changes (On et al. 2006). According to Piper (2003) the behavioural dimension includes signs and symptoms that reflect changes in performance of daily activities. This is in line with the description that the FIS evaluates the effects of fatigue on daily life activities in patients with chronic disease (Fisk et al. 1994).

Studies have described that patients with chronic disease and fatigue have difficulties in describing their experiences to nurses (Kralik et al. 2005, Ream et al. 1997). Nurses have difficulties in assessing fatigue (Tiesinga et al. 2002) and a poor concordance between
patients’ descriptions and documentation in the patients’ records has been reported (Ekman et al. 2002b). As a consequence fatigue might not be assessed or managed correctly. In order to improve communication about fatigue, routine questioning should be carried out so as to open up discussions, such as “Are you experiencing any fatigue?” If so, “How severe has the fatigue been during the past month?” Do you experience fatigue as a moderate or a severe symptom? If the fatigue is moderate or severe, a more in-depth assessment of performance of daily activities should follow. Here, the shorter version, FIS-25, the only one to our knowledge adapted for the patient group in focus could be valuable.

Methodological considerations
Internal validity concerns the design of the studies and to what degree the results of a study can be attributed to the independent variable. Threats to the internal validity include history, selection, maturation and mortality (Polit et al. 2003).

History threats are the effects of concurrent events that can affect the dependant variable (Polit et al. 2003). In studies I, II and IV, the data collection was performed on one occasion and concurrent events can not have occurred. In study III, patients were included over a four year period and there could have been, for example, a media campaign focusing on rehabilitation issues giving rise to history threats in the rehabilitation group. However, since this is a randomised study, the events are likely to affect both groups.

The selection threat focuses on bias arising from systematic differences between two groups (Polit et al. 2003). The patients in samples 1 and 2 were all registered patients, diagnosed as having COPD from four different geographical areas. The strength is that a large geographical area has been covered but the weakness is that the same physician did not diagnose the patients. The individuals selected from the population (samples 1 and 2) were randomly selected from the same geographical area as the patients (I, II, IV). In the comparison groups, the non response rate was between 55% and 58% (I, II). The results could have caused a slight overestimation of fatigue, functional limitations due to fatigue and health in the comparison group as it could be hypothesized that individuals experiencing fatigue are more motivated to answer a questionnaire about functional limitations due to fatigue. In the comparison group, the non respondents were older and there were more men among them (II). In the patient groups, there were no statistically significant differences between the respondents and the non-respondents with regard to age and gender (II). However, when
patients were compared with the individuals from the general population group, there were no differences between the two groups with regard to demographic data in one of the studies (I) while the patient group was older in the other study (II). Due to age differences, the groups were analysed using regression methods with imputation of age and group as covariates (II). The absence of statistical changes indicates that the selection bias is not a threat to the results. Study III was a randomised trial. In spite of that, there was a selection bias according to gender. This could be due to that the aim being to include 40 patients in each group. When the study was designed, the sample size was estimated using CRQ and 17 patients were required in each group. The estimation was doubled as there were no randomised studies that have used the FIS. The inclusion process has not fulfilled the calculation of the eligible patients that was performed when the study was designed. The power in study III is low, in relation to the sample size. For example, the power to find a significant treatment effect of 7.3 scores on the FIS total scores: A minimum sample size of 200 would have been required to increase the power to an acceptable level of approximately 80%. Nevertheless, as the comparison of baseline variables did not show any significant differences between women and men, the effects of rehabilitation were analysed both as mean differences between groups and differences of the mean changes within the groups. In study IV, the non-response rate was 41%. Although this is high, non response rates exceeding 50% are rare (Nakash et al. 2006). The difference between respondents and non-respondents was not significant with regard to gender but was significant with regard to age. The non-respondents were younger in both the test and the retest of the questionnaire. Since these age differences were only two years, although statistically significant, they are probably not a threat to the selection bias. The questionnaire has been validated in a patient group that is representative of the groups of patients studied in this thesis.

The maturation threat arises from processes occurring within the subjects as a result of time (Polit et al. 2003). Studies I, II and IV had descriptive designs. In study III, the effects of an intervention during a period of 12 weeks were followed up. Although one could envisage that, for example, the patients’ pulmonary function could worsen with time, decline in pulmonary function is a slow process and since the design was randomised, the maturation threat can be ignored.

External validity refers to the generalizability of the results of the research to other settings or samples (Polit et al. 2003). The results from studies I, II and IV are based on samples that
include all patients, 75 years of age or younger during a specific time period from four outpatients’ departments; two university hospitals, one central hospital and one district hospital, which strengthens the external validity. These patients probably represent patients with moderate and severe fatigue. Patients from out patients’ departments can not be generalized to patients with COPD, since we do not know, for example, how patients in primary care experience fatigue and the impact of fatigue. The results from the comparison groups from the general population can not be generalized to the general population, since these groups were randomized according to the patients’ gender and age in the relevant groups (I, II). The results from study III are based on one sample from one outpatient department and, as the sample size is small, the results can only be considered valid for the patients involved. Anyhow, many of the patients did not meet the inclusion criteria (39%) and thus the study sample is an exclusive part of a group of patients at the outpatients’ department. The inclusion criteria are not representative of an outpatient group. Results from recent studies (Lacasse et al. 2006), indicate that inclusion criteria should not involve pulmonary function \textit{per se} but rather the symptom and functional status, as these can be affected by rehabilitation. In study IV, the validation resulted in a reduction of items and therefore the shorter version of FIS needs to be validated on a new group of patients with COPD.
CONCLUSIONS

Almost half of the patients with COPD had problems with fatigue every day and experienced fatigue as a severe symptom.

Patients with severe fatigue have more functional limitations due to fatigue and worse health compared with patients who reported fatigue as a moderate symptom.

Patients with COPD experience greater severity of fatigue, more functional limitations due to fatigue and worse health compared with individuals from the general population.

No effects were seen on fatigue, functional limitations due to fatigue and health between patients who had undergone 12 weeks of pulmonary rehabilitation and controls.

After 12 weeks of pulmonary rehabilitation, the patients who had undergone rehabilitation improved their walking distances, performance and satisfaction with regard to their own selected daily activities.

The pulmonary rehabilitation programme, including exercise training twice a week and health education in how to effect behavioural changes, given by the different health care personnel in two to three sessions, might not be sufficient to reduce fatigue and functional limitations due to fatigue.

A shorter version of the Fatigue Impact Scale has been developed and adapted for the patients with COPD, which ought to be more relevant to this group of patients.
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REFERENCES


Physical dimension (PH)
PH10 Because of fatigue I am more clumsy and uncoordinated
PH13……¹ I have to be careful about pacing my physical activities
PH14……¹ I am less motivated to do anything that requires physical efforts
PH17……¹ I have trouble maintaining physical effort for long periods
PH23……¹ My muscles feel much weaker than they should
PH24……¹ My physical discomfort is increased
PH31……¹ I am less able to complete tasks that physical effort
PH32…………¹ I worry about how I look to other people
PH37……¹ I have to limit my physical activities
PH38……¹ I require more frequent or longer periods of rest

Cognitive dimension (CO)
CO1……¹ I feel less alert
CO5……¹ I have difficulty paying attention for a long period
CO6……¹ I feel like I cannot think clear
CO11…..¹ I find that I am more forgetful
CO18….¹ I find it difficult to make decisions
CO21….¹ I am less motivated to do anything that requires thinking
CO26….¹ I am less able to finish tasks that require thinking
CO30….¹ I find it difficult to organize my thoughts when I am doing things at home or work
CO34…..¹ I feel slowed down in my thinking
CO35….¹ I find it hard to concentrate

Psychosocial dimension (PS)
PS2. ……¹ I feel that I am more isolated from social contacts
PS3. ……¹ I have to reduce my workload or responsibilities
PS4……¹ I am more moody
PS7……¹ I work less effectively (this applies to work inside or outside the home)
PS8. ……¹ I have to rely more on others to help me or do things for me
PS9……¹ I have difficulty planning activities ahead of time
PS12……¹ I am more irritable and more easily angered
PS15……¹ I am less motivated to engage in social activities
PS16……¹ My ability to travel outside my home is limited
PS19……¹ I have few social contacts outside of my own home
PS20. ……¹ Normal day-to-day events are stressful for me
PS22……¹ I avoid situations that are stressful for me
PS25……¹ I have difficulty dealing with anything new
PS27….¹ I feel unable to meet demands that people place on me
PS28……¹ I am less able to provide financial support for myself and my family
PS29……¹ I engage in less sexual activity
PS33……¹ I am less able to deal with emotional issues
PS36……¹ I have difficulty participating in family activities
PS39……¹ I am not able to provide as much emotional support to my family as I should
PS40……¹ Minor difficulties seem like major difficulties

¹ = Because of fatigue