Outcome assessment in inpatient pulmonary rehabilitation: clinical results and methodological aspects
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General introduction
While you’re there, could you research ..., too, and make copies of all the information you find, and maybe underline the important parts for me, and sort of outline it, so I wouldn’t have to read it all?

Bill Watterson
1.1 Background

Patients with asthma or chronic obstructive pulmonary disease (COPD) often experience severe disabilities and handicaps despite optimal medical treatment. Outpatient pulmonary rehabilitation has proven to be an effective treatment in most of these patients [1-5], by reducing breathlessness and improving health status and functional exercise tolerance. The somatic severity is often complicated by psychosocial problems such as anxiety, depression, relational and/or occupational problems. The disabilities and handicaps contribute to the high burden of disease, resulting in a highly impaired health status. The main characteristics of severity are an unstable disease pattern and a high burden of disease. An unstable disease pattern is characterized by frequent hospitalization, recurrent exacerbations, a high medication usage, somatic comorbidity and/or severe deconditioning. Standardized treatment programmes, such as most outpatient and home rehabilitation programmes [6-9], may not meet all the needs of highly impaired patients [10] and seem not to be sufficient in severely dyspnoeic patients [11].

In patients with asthma or COPD who experience these somatic and psychosocial problems, a multidisciplinary inpatient pulmonary rehabilitation program (IPR) with treatment goals tailored to the individual and specific problems of a patient may be necessary. This thesis deals with the measurement of outcome of the multidisciplinary IPR program of Asthmacenter Heideheuvel in Hilversum, the Netherlands. The focus of this thesis lies on both the clinical outcome and the methodological difficulties of outcome assessment.

The current chapter describes the basic topics of asthma and COPD: definitions and clinical features, epidemiology, comorbidity, exercise limitation, psychosocial functioning, health status and treatment options. The remainder of this chapter includes an overview of the methodological difficulties of outcome assessment in pulmonary rehabilitation, a description of the IPR programme of Asthmacenter Heideheuvel, and concludes with the research questions.

1.2 Definition and clinical features of asthma and COPD

Asthma and COPD are both chronic airways diseases. Although they share some features, such as airflow limitation, these diseases are quite distinct in pathophysiology and epidemiology.
1.2.1 Definition of COPD

Chronic obstructive pulmonary disease, abbreviated as COPD, is characterized by the presence of slowly progressive, largely irreversible chronic airflow limitation [12;13]. COPD encloses chronic bronchitis and emphysema. Chronic bronchitis is clinically defined as the presence of chronic productive cough for 3 months in each of two successive years, which cannot be attributed to other pulmonary or cardiac causes. Emphysema is defined anatomically as an abnormal, permanent enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls. The primary cause of COPD is cigarette smoking [13;14]. Smokers have higher death rates, more respiratory symptoms and a greater annual decline of forced expiratory volume in one second (FEV₁); age of starting, total pack-years and current smoking status are predictive of COPD mortality. Socioeconomic status has been suggested as the second most influential factor on morbidity and mortality of COPD [15]. Other less important risk factors are passive smoking, ambient air pollution, hyperresponsive airways, and occupational exposure [13]. COPD is characterized by chronic inflammation throughout the airways, which is caused by cigarette smoking and possibly also by other COPD risk factors. This inflammation, together with an imbalance of proteinases and antiproteinases in the lung, and oxidative stress, are held responsible for the damaging of lung structures [14]. The only known genetic abnormality that causes COPD is alpha₁-antitrypsin deficiency, which accounts for less than 1% of all COPD cases [13].

The normal decline in FEV₁ in nonsmokers is 25 to 30 ml per year beginning at age 35. Smokers have a greater decline, up to 150 ml/year in susceptible persons. A small amount of lung function is regained after cessation of smoking, while the decline in FEV₁ becomes almost similar to that in nonsmokers [16]. Usually, patients with COPD have been smoking at least 20 cigarettes per day for 20 or more years before symptoms develop. The major symptoms of COPD are breathlessness (dyspnea) at exercise or even at rest, chronic cough and sputum production. A history of repeated respiratory infections is common [12]. With disease progression, intervals between acute exacerbations become shorter; weight loss, deconditioning, hypoxemia, pulmonary hypertension and cor pulmonale may develop [13].

1.2.2 Staging of COPD

The classification of the severity of COPD by the European Respiratory Society (ERS) is based on reduced FEV₁, expressed as a percentage of reference values [17]. A FEV₁ % predicted of ≥70 in combination with obstruction assessed as FEV₁/vital capacity % predicted less than 88% is classified as mild; a FEV₁ % predicted of 50-69 as moderate; and a FEV₁ % predicted of ≥50% as severe [12]. The American Thoracic Society (ATS) uses a different staging: stage I = FEV₁ ≥50% predicted; stage II = FEV₁ 35 to 49% predicted; stage III = FEV₁ ≥35% predicted [13]. Recently, the Global Initiative for Obstructive Lung Disease
(GOLD) proposed a new classification based on both FEV\textsubscript{1} and symptoms [14]. Asthmacenter Heideheuvel uses the ERS-classification. These stagings are all based on FEV\textsubscript{1}, because decrease in FEV\textsubscript{1} has long been known to be the best correlate with mortality and morbidity in patients with COPD [13]. However, disability is only weakly related to measurements of lung function [18]. A number of studies have shown that dyspnea is a better predictor of health status, morbidity and mortality than lung function parameters [19-23]. Nishimura showed that dyspnea is a better predictor of 5-year survival than FEV\textsubscript{1} [22]. Hajiro found that the Medical Research Council (MRC) dyspnea scale, but not the ATS-staging, separated different levels of health status [21]. Williams and Bury found that the MRC scale could distinguish between levels of disability as measured with the Sickness Impact Profile [19]. Health status was much stronger correlated to dyspnea (as measured with the baseline dyspnea index) ($r=0.51$ to $0.70$) than lung function measures ($r=0.08$ to $0.44$) in the study by Mahler et al. [24]. Furthermore, Almagro and coworkers found that not FEV\textsubscript{1} %predicted or FVC %predicted, but quality of life, depressive symptoms, comorbidity, marital status and prior hospital admissions were associated with higher mortality [23]. Several authors argued to use dyspnea for grading severity [11;18;21;22]. Wedzicha and coworkers suggested the MRC dyspnea scale as a valid and simple method for categorising disability, as a complement to FEV\textsubscript{1} in the classification of COPD severity [11;18]. They found significant associations between MRC grade and walking distance, quality of life, mood state and activities of daily life. The value of the MRC scale as a tool for grading disease severity should be further studied in prospective studies.

1.2.3 Definition and staging of asthma
Asthma is defined as a chronic inflammatory disorder of the airways, which causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night and in the early morning [25]. These episodes are usually associated with variable airflow obstruction which is often reversible: spontaneous or with medication. Airway hyperresponsiveness is an important feature of asthma, leading to clinical symptoms of dyspnea and wheezing. The recurrent airflow limitation in asthma is caused by a variety of changes in the airway [25], including acute bronchoconstriction caused by allergens, nonsteroidal anti-inflammatory drugs (such as aspirin) or stimuli as exercise, cold air and irritants. The airflow limitation is mostly accompanied by airway edema and chronic mucus plug formation, whereas in long-lasting asthma airway remodelling occurs. Severe chronic asthma can lead to persistent airflow limitation [25]. The reversibility of the airflow limitation, either partial or complete, is a major difference between asthma and COPD. Because of the difficulty in differentiating patients with asthma whose airflow obstruction remits only partly, from patients with COPD and airway hyperreactivity, patients with
unremitting asthma can also be classified as having COPD [13]. The 1992 three-step severity classification of asthma (mild, moderate, severe) is based on clinical symptoms, airflow limitation and level of medication necessary for stabilisation [26]. The most severe feature determines the level of severity. The most recent guideline report [25] has a new four-step classification based on symptoms, nighttime symptoms and airflow limitation, distinguishing between mild intermittent, mild persistent, moderate persistent and severe persistent asthma. Asthmacenter Heideheuvel used the 1992 three-step severity classification during the study period.

1.3 Epidemiology of asthma and COPD

A major difference between asthma and COPD is the age-period with the highest incidence and prevalence. Asthma often begins in childhood; the incidence of adult-onset asthma is much lower [25]. COPD is typically caused by cigarette smoking for about 20 years and is strongly associated with age [13]. It is difficult to give a clear picture of the prevalence of asthma and COPD, due to differences in diagnostic criteria used by various sources [27]. In the Netherlands, the prevalence of asthma is about 11.6 per 1000 for women and 10.8 per 1000 for men [28]. The prevalence of COPD is much higher: 24.2 per 1000 for men and 13.8 for women. The overall prevalence of chronic airflow limitation increased from 17% in 1977 to about 31% in 1992, including an increase in prevalence of severe cases from 2% to 4% [29].

In Europe COPD and asthma are, together with pneumonia, the third most common cause of death. COPD is the fourth leading cause of death in North America [30;31]. Mortality rates of obstructive lung disease (including both asthma and COPD) in the United States of America have increased 47% from 1979 to 1993 [32]. Mortality rates of obstructive lung disease have started to stabilise among men, but continue to increase among women, which reflects historical smoking trends in these populations [32]. In the Netherlands, the mortality rate (per 100,000 persons) for asthma was 0.4 for men and 0.3 for women in 1994 [28]. The mortality rate for COPD was much higher: 50.2 for men and 23.5 for women. Mortality from asthma in adults showed a large decline since 1990 [33]. Mortality from COPD increased significantly except for men aged 35-64 years, who showed a significant decrease. Older women (>65 years) showed a very large increase from a standardized mortality rate of 100 per million in 1980 to about 220 in 1994 [33]. In the Netherlands, asthma and COPD combined belong to the 10 leading causes of lost disability-adjusted life years [28]; worldwide, COPD ranked 12th in 1990 and is projected to be the 5th cause of lost disability-adjusted life years in 2020 [14].
1.4 Comorbidity in patients with asthma or COPD

Comorbidity in patients with asthma or COPD can be divided in two groups: a) other primary coexisting diseases and b) secondary diseases or impairments resulting from chronic airflow limitation. Recently, Van Manen and coworkers [34] studied the prevalence of comorbidity in adult patients with asthma or COPD and controls selected from general practices in the Netherlands, using a questionnaire on 23 chronic diseases with a prevalence of ≥2%. This study showed that the prevalence of comorbidities was 10 - 12% higher in patients with chronic airflow limitation, with significantly higher odds ratios for locomotor diseases (prevalence 36.1%), sinusitis, migraine, depression, insomnia, stomach/duodenal ulcers and cancer. The prevalences of hypertension and heart disease were high (22.7% and 13.1% respectively) but did not differ between patients with chronic airflow limitation and controls.

In patients with asthma, allergy-related problems and anxiety are common [25]. In long-term users of oral corticosteroids, osteoporosis may occur [35]. COPD is associated with a range of non-pulmonary problems: exercise limitation, social isolation, altered mood states (anxiety and depression), muscle wasting, and weight loss [14]. Hypoxemia has neurocognitive effects: higher levels of hypoxemia are related to more severe impairment of neuropsychological functioning [36]. Hypertension, diabetes mellitus and ischemic heart disease were the most common comorbid diseases in a study on mortality of patients with severe COPD after an acute exacerbation [37]. Ferrer and coworkers found that 84% of a sample of outpatients with COPD reported at least one coexisting chronic condition, with 41% reporting three or more comorbidities [38]. Osteoarthritis was the most prevalent condition. Kaiser et al. found 75% self-reported multimorbidity in a group of patients with asthma or COPD [39].

1.5 Physical performance

The reduction of physical activity is one of the major characteristics of chronic airflow limitation [40] and is extensively studied in patients with COPD. Exercise intolerance is the most disabling and distressing consequence of chronic airflow limitation for most patients [41]. Casaburi describes a downward spiral: the breathlessness associated with activity causes patients to become sedentary, which in turn deconditions the muscles of locomotion [44]. This in turn makes physical activity even more unpleasant and thus reinforces the sedentary lifestyle. In contrast to healthy persons, exercise capacity in patients with COPD is limited by the maximal level of ventilation they can sustain [42]. No interference with physical performance may occur at minor or moderate obstructions, because normally a
marked ventilatory reserve is present at maximal exercise. Exercise capacity is often limited by symptoms (dyspnea and fatigue) prior to physiological limitations [43]. The major causes of decreased exercise capacity are airflow obstruction (limiting the maximal ventilation and distorting pulmonary gas exchange) [44] and peripheral skeletal muscle dysfunction. The major characteristics of peripheral muscle dysfunction are reductions of muscle mass and muscle strength [45-49], together with reduction of oxidative enzymes and altered fibre type profiles [49]. Peripheral muscle dysfunction is mainly caused by the lack of physical activity: patients avoid exertion because of their fear of dyspnea. Muscles may also be affected by malnutrition [50], hypoxia, hypercapnia and drug therapy [49]. Other factors limiting exercise tolerance include impairment of respiratory mechanics, requiring more effort of the respiratory muscles, which in turn causes inspiratory muscle fatigue [51;52] and circulatory impairments, such as destruction of the pulmonary vasculature and right heart decompensation [41;44;51]. The destruction of alveolar walls and pulmonary vasculature causes a decrease of the effective area for gas transport, resulting in a diffusion disorder.

In patients with asthma, exercise may induce constriction of the airways, which may cause not only dyspnea, but may also trigger an asthma attack [53;54]. Therefore, patients with asthma often avoid physical activity, resulting in the deconditioning spiral described above.

1.6 Psychosocial functioning in patients with asthma or COPD

The most prevalent psychosocial problems in patients with chronic airflow limitation are anxiety and depression. Several studies reported on the prevalence of anxiety and/or depression in patients with asthma or COPD [55-58]. In patients with COPD, the prevalence of depression ranges from 16% [59;60] to 74% [61]; the prevalence of anxiety shows an ever wider range: from 2% [55] to 96% [61]. The differences in prevalences between studies are most probably caused by differences in patients samples and measurement methods [36]. Patients with COPD have higher levels of anxiety and depression than controls or normal subjects [62-64], but do not seem to have more personality disorders than normal subjects [65]. The increased risk of depression in patients with COPD has recently been questioned in a systematic review [66]. This review found an association between depression and COPD, but concluded that the empirical evidence on increased risk of depression remains inconclusive due to the poor methodological quality of the included studies.

In patients with asthma, anxiety plays an important role. A major characteristic of asthma is sudden and unexpected attacks of impaired breathing [67]. This threat is accompanied
by anxiety. On the one hand, asthma-specific anxiety (as opposed to general anxiety) is important in emergency compliance, by influencing the amount of medication taken by the patients and by influencing decisions about seeking medical attention [67]. On the other hand, adequate disease behaviour may be compromised by very strong anxieties such as panic disorders, over- or underestimation of asthma symptoms and unfounded fear of side effects [67]. Furthermore, psychological stress influences the immune system and the autonomic control of airways and increases the risk of respiratory infections [68]. Although the level of anxiety in patients with mild asthma does not seem to differ from the general population [69;70], psychopathology plays an important role in severe asthma. Bosley reported that about 40% of the patients with near-fatal asthma attacks were psychiatric cases according to the General Health Questionnaire [71]. Adverse psychological and social factors are related to asthma deaths [72]. Ten Brinke and coworkers recently reported an association between health care utilization and psychological functioning in patients with severe asthma (defined as a high dose of inhaled corticosteroids and at least 1 severe exacerbation in the last year) [73], also using the General Health Questionnaire to detect psychiatric disorders. Psychiatric cases had higher odds ratios than non-cases for ≥4 visits to general practitioner, ≥2 emergency visits, ≥2 severe exacerbations and for ≥2 hospital admissions (all in the last year).

Depression seems common in patients with asthma: Mancuso et al. reported that 45% of a sample of younger adults with asthma in primary care had depressive symptoms [58]. Dyer et al. reported a high level of depression in older hospitalized patients with asthma (48%), although not significantly different from hospitalized controls [74].

1.7 Health status

Chronic airflow limitation has a large impact on the life of a patient. The impact of disease on patients' life, health and well-being can be described and quantified by health status measurement [75;76]. The term health status is often used interchangeably with functional status and with health-related quality of life [76-78]. Functional status reflects the ability to perform tasks of daily life [77-79]. Health-related quality of life assesses the consequences of a disease, and encompasses the physical, psychological and social functioning of a patient [80]; it connotes the subjective experience of the impact of health status on the life of a person [77]. Quality of life is unique to each individual [81;82]. Perception of quality of life varies between persons and is dynamic within them [83]. Most existing measures of quality of life fail to take account of this uniqueness by imposing standardized models of quality of life and preselected domains [81]. This neglects that people have different expectations of their health, that people may be at different points on their illness trajectory
and that the reference value of their expectations may change over time ("response shift" [84]) [83]. Therefore, most currently available instruments measure health status rather than quality of life [81;82;85] and may be inappropriate for measuring quality of life [86].

1.7.1 Health status measures
Health status measures can be divided into two groups: generic and disease-specific [87]. Generic measures can be divided into health profiles and utility measures; they can be used in a variety of clinical settings and populations and allow comparisons of health status across different diseases [77;87]. Disease-specific measures focus on the areas of function that are relevant to a particular illness [88], and are therefore more sensitive to small but important changes caused by treatment [77;88]. Using both generic and disease-specific measures in clinical trials is advocated by several authors [89-95].

The impairment of physical, psychological and social functioning in patients with asthma or COPD has been studied extensively. Several studies used the patient’s perspective to explore in which domains of life patients experience the most problems. Major problem areas are symptoms, restriction of day-to-day activities (because of dyspnea), physical problems and fatigue, emotional functioning, control over the disease, environmental exposure and (restriction of) social functioning [96-100]. This information has been used to construct disease-specific health status questionnaires, such as the Chronic Respiratory Questionnaire (CRQ) [89;101-103], the St. George's Respiratory Questionnaire (SGRQ) [104-106], the Quality of Life for Respiratory Illness Questionnaire (QoLRIQ) [100;107], the Asthma Quality of Life Questionnaire (AQLQ) [88;99] and a range of others [98;108-115]. Recent trends are the development of standardized versions of the CRQ [116] and the AQLQ [117]; the development of short or shortened questionnaires [114;118-124]; the construction of questionnaires specifically measuring activities of daily life in patients with COPD [125;126]; and the first attempts at disease-specific utility measures [127;128].

The impairment of health status in asthma and COPD has also been studied with several generic profile questionnaires, such as the Sickness Impact Profile (SIP) [129;130], the Quality of Well-Being scale [63], the Medical Outcomes Study Short Form-36 (SF-36) [131;132], the Rand-36 [133;134] (which slightly differs from the SF-36 in item summation, but not in wording or structure [135]) and the Nottingham Health Profile [136;137]. Overviews of generic measures are given by Bowling [138] and by König-Zahn [139].

1.7.2 Health status in COPD
Studies using the SIP showed that patients with COPD are significantly more impaired than controls in all domains of functioning [19;36;56;63;140;141]. 60% of the patients with chronic airflow limitation have severe functional limitations [19;56]. Recreational activities and household management are the most restricted domains [19;56;140;142;143]. Leidy
and Haase did a qualitative study on the functional performance of people with COPD and reported limitations in household maintenance, movement, family activities, social activities, (voluntary) work and recreation [144]. Williams and Bury reported that 40% of the patients in their study was unable to work due to illness [19]; Ketelaars and coworkers reported that most older patients with COPD have retired or stopped working [145].

Several studies assessed the determinants of health status in COPD. Health status is significantly related to symptoms such as breathlessness [19;56;142;146-148] and fatigue [149]; to exacerbations [150]; mood state including anxiety and depression [56;77;151-154]; activities of daily life [153] and health resource use [152;155]. Several studies show a relation between health status and exercise tolerance [56;145;151;152], but others find no relation [156;157].

The relation of health status with lung function parameters is less clear, with correlations ranging from 0.04 to 0.41 [75;77]. Health status is related to the severity of hypoxemia in patients with severe COPD [141]. Subjective fatigue dimensions (reduced activity and reduced motivation) are related to FEV₁; physical fatigue is related to muscle force [158]. Ferrer [38] and Hajiro [159] found that the ATS and British Thoracic Society severity stagings respectively, which are based on FEV₁, can separate groups of patients with varying degrees of impaired health status as measured with the SGRQ. However, Hajiro [21] found in an earlier study (which probably used largely the same patients) that the MRC-dyspnea scale, but not the ATS-staging, could separate levels of health status.

1.7.3 Health status in asthma

The most important impaired functional domains in asthma are symptoms, emotions, physical activities and environment [120]. Symptoms affect all domains of health status [160;161]. Asthma has impact on employment, education, physical activities, social interaction, personal realtionships and emotional well-being [162]. Health status is related to disease severity [161], as indicated by number and duration of episodes, lung function, medication use, presence of exacerbations, emergency care, hospitalizations [122], and symptoms. Lung function, as measured with FEV₁, shows small to moderate but significant correlations with most domains of the SF-36 [163]. Patients with a positive screen for depression have significantly worse scores on the SF-36 and the AQLQ than patients with a negative screen [58]. Health status in asthma is also influenced by gender (women having poorer health status) [98;99;160;164], socioeconomic status (patients with lower education report lower health status) [164;165] and ethnicity (ethnic minorities have poorer health status) [165;166]. Patients with moderate asthma have a poorer health status than the general population, as indicated by lower scores on several SF-36 domains: physical functioning, pain, general health perception and emotional role limitations [167]. Older adults with asthma have a poorer health status than controls: a lower self-assessment of
health, a greater handicap in mobility and more problems with instrumental activities of daily living [168]. Furthermore, elderly people with asthma have significantly lower scores than controls on several domains from the SF-36: physical function, physical role, vitality, health change and general health perception [74].

1.8 Treatment methods for asthma and COPD

1.8.1 Pharmacotherapy

The goals of treatment in asthma and COPD are to prevent respiratory symptoms and recurrent exacerbations and to preserve optimal lung function [12;25], with the ultimate goal of improving daily functioning and health status. In COPD, cessation of smoking is the best way to help the patient [169], because so far it is the only strategy that reduces the rate of decline in lung function [16]. However, less than a third of the smokers continue their abstinence after counselling [13]. The pharmacotherapy of breathing problems caused by asthma and COPD is quite similar. A distinction can be made between quick relief medication and long-term control medication [25]. Quick relief bronchodilation is achieved by β2-agonists and anticholinergics. β2-agonists are preferred in asthma [25], while new, more selective anticholinergics are the best choice in COPD [170]. Long-term control is mainly achieved with inhaled and oral corticosteroids which have a potent anti-inflammatory effect; with long-acting bronchodilators including β2-agonists, anticholinergics and methylxanthines (theophylline). In asthma, anti-allergic agents, such as nedocromil and chromolyn sodium, and leukotriene antagonists are also used for long-term control [25]. Inhaled corticosteroids do not alter the decline of FEV₁ in patients with COPD, but reduce the number of exacerbations and slow the decline in health status [171]. In patients with COPD and progressive hypoxemia, long-term oxygen therapy may be necessary and prolongs life [13]. Other noteworthy medications include influenza vaccination, psychoactive agents and cardiovascular therapy. In some patients with very advanced COPD, lung volume reduction surgery or lung transplantation may be indicated [169].

Exacerbations are the main cause of medical intervention and admission to hospital in patients with asthma or COPD [172]. Mild exacerbations can be defined as increased intensity/frequency of symptoms and/or worsened lung function (in asthma) or as increased breathlessness, associated with increased cough and sputum production (in COPD), forcing the patients to seek medical attention. Asthma exacerbations are severe if a lack of response or a quick progression occurs or if the patient is at risk of asthma-related death. COPD exacerbations are severe when associated with acute respiratory failure [172]. Treatment of exacerbations is done mainly with high dose systemic corticosteroids, supplemental
general introduction

oxygen, short-acting inhaled bronchodilators and, in case of bacterial infection, with antibiotics.

Long-term treatment with systemic corticosteroids may cause several adverse systemic effects, including osteoporosis, adrenal insufficiency, skin damage, cataracts, diabetes and secondary infection [13;35]. Long-term use of oral steroids should be weighed against the substantial adverse effects [35;173].

1.8.2 Pulmonary rehabilitation

The principal goals of pulmonary rehabilitation are to reduce symptoms, decrease disability, increase participation in physical and social activities, and improve the overall quality of life for individuals with chronic respiratory disease [4]. In recent years, several comprehensive and extensive guidelines on the components and results of pulmonary rehabilitation have been published [3-5;10;174-177]. Pulmonary rehabilitation may benefit all patients with lung disease who, despite optimal medical treatment, are dyspnoeic, have reduced exercise tolerance, or experience a restriction in activities [4]. The need for pulmonary rehabilitation is dictated by symptoms, disability, and handicap, not by the severity of airflow obstruction. Pulmonary rehabilitation is mainly offered to patients with COPD, but also patients with chronic asthma, bronchiectasis and pulmonary fibrosis may benefit. Rehabilitation becomes appropriate when patients become aware of their disability, which is usually at MRC dyspnea grade 3 or higher [5].

1.8.2.1 Definitions of pulmonary rehabilitation

Pulmonary rehabilitation is defined as a multidisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise physical and social performance and autonomy. American Thoracic Society, 1999 [4].

Pulmonary rehabilitation is a process which systematically used scientifically based diagnostic and treatment options to achieve the optimal daily functioning in health-related quality of life of individual patients suffering from impairment and disability due to chronic respiratory disease as measured by clinically and/or physiologically relevant outcome measures. European Respiratory Society, 1997 [10].

1.8.2.2 Settings and components

Pulmonary rehabilitation is effective in all settings, although programs vary considerably in content, intensity, and duration. Settings include hospital inpatient, hospital outpatient, community centre based, physio-practice based and home-based. The content may vary from exercise training [178] to comprehensive programs given by interdisciplinary working treatment teams (see §10). Most programs are between 4 and 12 weeks, but durations as
short as 10 days [179;180] to as long as 6 months [9] have been reported. Inpatient pulmonary rehabilitation is suggested for severely handicapped patients and for a number of special reasons, such as integrated 24-hour monitoring; specific interventions such as nutritional therapy, behavioural interventions to correct psychosocial problems, and teaching of coping skills; and logistic aspects such as travelling distance [10]. Patients referred to outpatient pulmonary rehabilitation programs should be in a stable phase of their disease, and have no major psychological or somatic problems. Furthermore, these patients should have enough functional ability to attend the hospital or community centre two or three times a week for an outpatient session with mainly exercise training [4;10]. This type of patients can also be referred to home-based or physio-practice based pulmonary rehabilitation programs [6-8;181;182]. Home-based rehabilitation is not suitable for severely disabled patients [11]. Contraindications for rehabilitation are a lack of motivation to participate in the programme, and diseases interfering with the treatment process [10;183].

Pulmonary rehabilitation programs should be comprehensive and individually tailored. The major components of rehabilitation are exercise training, education, psychosocial and behavioural interventions, and outcome assessment [4;184]. Physical training improves exercise capacity and health status. The physical training, mostly walking and cycling, should have a sufficient frequency, duration, and intensity to achieve a physiological training effect. The target level of exercise training intensity should be around 60% of the maximum work capacity. Exercise training should be done for about 20 to 30 minutes two to five times a week, with a course duration of 4 to 12 weeks [4;5]. Although a true physiological effect may only be achieved with a relatively high training intensity [185], improvements in functional performance may occur at lower intensities [186] because of improvements in confidence, ergonomics, or a reduction in dyspnea [184]. The effect of training is specific to the muscle groups that are trained, and reversible. Upper extremity endurance training may improve arm function which is important for many activities of daily living. Lower extremity endurance training, which is the major component of most pulmonary rehabilitation programs, improves submaximal endurance time for walking and cycling. Strength training is useful for reducing peripheral muscle weakness, which contributes to exercise limitation. Respiratory muscle training improves the strength and endurance of respiratory muscles, but has no impact on disability or handicap.

Patient education has become a central feature of pulmonary rehabilitation, although education alone is not sufficient [60;187;188]. Education includes lectures about medication and pathophysiology of lung disease; personal advice on nutrition, smoking cessation, travel and relationships; and training of self-pacing, relaxation, energy conservation, chest clearance and adequate self-management skills [4;5;10]. The role of breathing retraining remains unclear. Nutritional therapy, which can consist of advice,
nutritional supplements and anabolic agents, is often necessary because of weight loss and depletion of fat-free mass, especially in patients with COPD admitted to inpatient programs [189]. Obesity may be a problem in a number of patients. Psychosocial and behavioural interventions are necessary to deal with anxiety, depression, coping problems, and reduced self-efficacy. Patients should be helped to cope more effectively with the physical manifestations and psychological consequences of their illness [10]. Fear of dyspnea-producing activities may cause patients to avoid doing their daily activities. Anxiety, decreased energy levels and depression may interfere the ability of patients to cope with their illness, resulting in inadequate illness behaviour. Interventions, in the form of educational sessions, or individual, family and group psychological counselling [190], may include behavioural modification, stress management, panic control, muscle relaxation, goal setting and rewarding, changing beliefs about exercise and health related behaviour, personal relationships and sexuality. Group discussions about common symptoms, concerns and problems may give emotional support. The last component of pulmonary rehabilitation, outcome assessment, is described in detail in § 1.9.

1.8.2.3 Benefits of pulmonary rehabilitation
The major benefits of pulmonary rehabilitation in patients with COPD are a reduction in symptoms, especially breathlessness; and improvement of health status and functional exercise capacity [1-5;191]. Impairment of lung function does not improve with pulmonary rehabilitation and should therefore only be used as a descriptor of the patient population. Improvement of health status, daily functioning and physical performance has been reported by a host of studies on outpatient pulmonary rehabilitation, both randomised controlled trials [9;11;60;192-198][199;200] and non-randomised or observational studies [157;201-217]. Positive effects have also been reported in physio-practice based [8;218] and home-based pulmonary rehabilitation programs [6;7;181;182]. However, severely disabled patients, with a maximal MRC dyspnea score, do not benefit from rehabilitation at home [11]. Improvements in psychological and cognitive functioning have also been reported [190;194;203;207;209;219].

The short-term benefits of inpatient pulmonary rehabilitation have been reported in a number of observational studies [179;180;220-236]; until now only one randomised controlled trial of comprehensive inpatient pulmonary rehabilitation versus standard care has been published [237]. In contrast to the previous studies, no short-term improvements in psychological, physical, social or practical functioning (all assessed with questionnaires) were found in a randomized trial of inpatient pulmonary rehabilitation with or without patient education [238].
1.8.2.4  **Long-term effectiveness of pulmonary rehabilitation**

Most studies on the long-term effectiveness of pulmonary rehabilitation show lasting improvements, but gradual deterioration is also found, especially in inpatient rehabilitation. The research synthesis by Cambach and coworkers found significant effect sizes for maximal exercise capacity and 6-minute walking distance up to 9 months [1]. Several outpatient programs have shown sustained improvement in exercise capacity at 6 months [8;193;197] and 12-36 months post-rehab [7;9;196;202;210;239-241] and in health status [8;9;197;242]. Others found that some or all gains made in disability and handicap gradually decreased during follow-up [243;244], but remained significantly positive when compared to control groups [195;196;210]. Several long-term studies on inpatient pulmonary rehabilitation show marked deterioration in the follow-up period [224;229;230;245], but others found sustained improvement [180;246] or both deterioration and sustained improvement [220;221]. The only randomized controlled trial found that the rehabilitation group was still significantly better than the conventional care group at 24 weeks (16 weeks post-rehab) [237], despite deterioration in the community-phase of the study [247].

1.8.2.5  **Effect on hospitalisation**

Pulmonary rehabilitation reduces the number of hospitalisations and the number of days in hospital [3;195;242;248]. However, some studies found no change in hospital admissions after outpatient [196] or inpatient pulmonary rehabilitation [246]. Until now, only two full economic analyses of pulmonary rehabilitation have been published [249;250]. Results show that comprehensive outpatient [250] and inpatient pulmonary rehabilitation [249] and behavioural programs [251] produce quality-adjusted life-years within bounds considered cost effective. Several recent studies reported the cost of the program [9;199;208;217;252], but without any subsequent cost-effectiveness analysis [253].

1.8.2.6  **Further research**

Further research is required on the essential components of pulmonary rehabilitation [4], especially on optimal types and intensity of exercise training, patient education and psychosocial and behavioural interventions [174;254]. The optimal duration and intensity of both outpatient [198] and inpatient programs is unknown. Ringbaek and coworkers found that exercise and education twice a week for 8 weeks did not result in improvements [252]; Engström et al. found improvement in exercise capacity but not in health status with 2 sessions per week [241]. However, others found significant improvements with one [208] or two sessions per week [192;210;211;213]. Most outpatient programs use 3 sessions per week, but programs of 5 days a week have also been reported [194;203]. Duration of
outpatient programs range from 4 weeks [198] up to 6 [9] and 12 months [241]. Green and colleagues found that a 7-week program gave significantly greater improvements than a 4-week program [198]. Exercise maintenance results in sustained improvements in exercise capacity [6;202;212]. However, the optimal form of maintenance programs [254-256] and the usefulness of aftercare [232], booster sessions [241] and repetition of pulmonary rehabilitation [242] need to be studied. This is especially important in inpatient pulmonary rehabilitation, because of the frequently reported deterioration post-rehab. More research is also required on pulmonary rehabilitation in lung diseases other than COPD [4] and in clinically unstable patients. There is some evidence that patients with asthma benefit from pulmonary rehabilitation [8;53;195;225;248].

1.8.2.7 Outcome of IPR in Asthmacenter Heideheuvel

The patients referred to the IPR-program of Asthmacenter Heideheuvel are often severely impaired and clinically unstable, as characterized by recent hospital admissions, recurrent exacerbations, and somatic and/or psychosocial comorbidity. This differs from most other inpatient and outpatient pulmonary rehabilitation programs, which exclude unstable patients. Another difference is that not only patients with COPD, but also patients with asthma are referred for treatment. Until now, nothing is reported about the results of IPR in patients with asthma or in patients with unstable COPD. Therefore, the short- and long-term outcome of interdisciplinary inpatient pulmonary rehabilitation for patients with asthma or COPD in Asthmacenter Heideheuvel is described in chapters 2 and 3 of this dissertation. Because of the comprehensive nature of the rehabilitation programme, outcome assessment included health status, hospitalization, medication usage, functional exercise tolerance, psychosocial functioning and coping behaviour.

1.9 Measurement of outcome in pulmonary rehabilitation

Jones [75] describes COPD as a multisystem disorder. The major components are breathlessness, fatigue and muscle wasting, exacerbations, sleep and mood disturbances. There is a complex interplay between breathlessness, exercise limitation, depression and anxiety, muscle wasting and disability [105;257], which cannot be assessed with measures of impaired lung functioning [75]. The major goals of pulmonary rehabilitation are to reduce symptoms, increase function and improve health status [258]. Outcome measurement should be as comprehensive as both the disease and the program, using appropriate and sensitive measures.
The focus of outcome measurement in pulmonary rehabilitation has shifted from mortality and FEV$_1$ towards health status. Until about a decade and a half ago, clinical aspects such as mortality and FEV$_1$ were the predominant outcome parameters of pulmonary rehabilitation. The review by Petty in 1993 describes the outcome of pulmonary rehabilitation only in terms of survival [259]. In the 1980's, exercise tolerance became the most important outcome variable. Far more complete overviews of outcome assessment in pulmonary rehabilitation are given by Fishman (1994) [260], Zuwallack (2000) [258] and others [261;262]. Outcome measurement in pulmonary rehabilitation should include health status; survival; physical functioning (including exercise performance and functional status); medical resource consumption (ie. hospitalizations and use of emergency care); respiratory symptoms, especially dyspnea; frequency of exacerbations of disease; psychological well-being [263]; care-giver burden; need for assistive devices; nutritional status and body composition. Pulmonary rehabilitation hardly ever changes airflow limitation, hyperinflation, and disturbances in gas exchange. Therefore, objective measurement of pulmonary function, which is necessary for describing patients and for assessing outcome of other treatment options such as medication and assistive devices, has no place in the outcome measurement of pulmonary rehabilitation.

1.9.1 Health status measurement in pulmonary rehabilitation

Health status measurement provides a comprehensive estimate of the primary and secondary effects of disease [75]. In the last 15 years, a large number of health status measures specific for asthma and/or COPD have been published (see §7.1). There are several reviews available on the use of both disease-specific and generic health status measures in asthma and COPD [75;76;85;91;93;94;105;264;265]. In recent years, several comparisons of disease-specific and/or generic health status measures have been published [95;128;153;167;266-274]. Disease-specific measures are consistently more responsive, more valid, more reliable and better discriminators than generic profile (SF-36, SIP) and utility measures (Euroqol or EQ5D [275], rating scale, standard gamble). The AQLQ performs best within the asthma-specific measures [128;266;274]. Within the COPD-specific measures, both the CRQ and the SGRQ perform good [267;270]. The CRQ is more responsive to change due to pulmonary rehabilitation than the SGRQ and the BPQ [273;276], although Yohannes et al. suggested that the BPQ provides a more valid assessment of health status than the CRQ in elderly patients with COPD [153]. The SF-36 performs moderately good [95;128;267]. The validity of utility measures for measuring health status in patients with asthma or COPD is questionable [128;266].

1.9.2 Measurement of physical performance in pulmonary rehabilitation

The aspect of physical performance about which information is needed, determines the
type of assessment of exercise limitation. The maximal exercise test, mostly performed on a bicycle ergometer with a progressive increase of workload, gives detailed information on the maximal workload and the type of impairment limiting the physical exercise ability [41, 277, 278]. Certainly when arterial blood gases are obtained, limitations can be analysed as predominantly ventilatory, circulatory or metabolically based. Maximal exercise testing can also be used for determining the optimal exercise training intensity [40, 51, 279]. However, because most patients with airflow limitation seldom perform activities near their maximal capacity, assessment of submaximal or functional exercise tolerance will give a more realistic picture of the ability of a patient to perform daily activities. This is mostly done by some kind of walking test [280, 281], because walking is a major life activity. The most widely used tests are a self-paced 6- or 12-minute walking test [282, 283], which is based on the run test by Cooper [284], or a controlled-pacing incremental test (shuttle walk test [285, 286]). Compared to traditional laboratory tests such as cycle or treadmill ergometry, walking tests require minimal technical expertise and equipment and are less demanding for the patient. However, timed self-paced walking tests are dependent on effort, motivation and strategy [280]. There is a large effect of encouragement [287] and a learning effect [288, 289]. Further disadvantages include the non-standardized use of the test (despite the availability of a protocol [283]) and the dependance on a single measure for outcome [280, 283]. To overcome some of these problems, Singh et al. developed the shuttle walking test [285, 290]. This is an incremental, standardized field walking test that provokes a symptom limited maximal performance. Because endurance capacity is important for most activities of daily living, the endurance shuttle walk test has been developed by the same group to complement the incremental test [286]. The endurance shuttle walk is far more sensitive to change than the incremental shuttle test [286], which makes this test very useful for measuring outcome in pulmonary rehabilitation. Change in endurance capacity can also be measured reliably with constant-load submaximal exercise testing on a cycle ergometer [3, 8, 291], but only when a sufficient maximal duration (>20) and intensity (60-70% of the maximal workload of a patient) are chosen.

The problem of using a single outcome measure, while the limitation of physical performance is multifactorial, is investigated in chapter 5 of this dissertation. This is done by incorporating more factors than maximal distance in the outcome of the self-paced 6-minute walking test (oxygen desaturation, maximal heart rate, perceived breathlessness).

1.9.3 Remaining methodologic problems
Several methodologic problems with outcome research in pulmonary rehabilitation remain. First, the content and comprehensiveness of outcome measurement should represent the content and comprehensiveness of the treatment. Much outpatient and home-based pulmonary rehabilitation programs comprise mainly exercise training with some disease
education. For these programmes, a disease-specific health status questionnaire, a measure of dyspnea and a walking test may be sufficient to capture the results of the treatment [4]. However, the content of currently existing outcome measures does not represent the content of inpatient pulmonary rehabilitation adequately. Standardized questionnaires and function tests do not allow for differences in problems, for differences in treatment goals, or for differences in importance of problems and treatment goals. Therefore standardized questionnaires and function tests can not correctly show the outcome of inpatient pulmonary rehabilitation with individualized or personalised treatment goals. Individual assessment of change is almost non-existing in pulmonary rehabilitation, except for the dyspnea domain from the CRQ. Furthermore, multi-intervention treatments such as inpatient pulmonary rehabilitation, require multi-outcome measurement [292]. Measurement of outcome on the level of patient-specific treatment goals is necessary in individualised treatment. Chapter 7 of this dissertation describes an attempt at individualised, treatment-goal related outcome measurement.

The second problem is that observed change is difficult to interpret because the size of a minimal clinically important difference is still unknown in most questionnaires and function tests. From all outcome measures used in pulmonary rehabilitation, only the CRQ [293-295], the AQLQ [296;297], the SGRQ [104;298] and the encouraged 6-minute walking test [299] have an established threshold for clinically relevant change. Chapter 6 of this dissertation describes the longitudinal measurement properties of the Quality of Life for Respiratory Illness Questionnaire [100], the health status measure used for measuring the outcome of the inpatient pulmonary rehabilitation program of AsthmaCenter Heideheuvel (see chapters 2 and 3). A range of both anchor-based [293;296] and distribution-based methods [300-302] are used in this study to compute the minimal important difference [303;304]. Chapter 6 also goes into detail on the validity of anchor-based computation of the minimal important difference, which has been questioned by several authors [305-307].

A separate methodological problem is that clinical studies are often hindered by attrition or dropout of patients. A number of studies on IPR, including the study described in chapters 2 and 3, suffer from dropout of 40 to 60% of all patients, which threatens both the internal validity of the study and the generalizability of the study findings. Therefore, a method was developed to test the robustness of the findings, by combining imputation of missing data with sensitivity analysis. This is presented in chapter 4.

1.10 Description of the inpatient treatment programme in AsthmaCenter Heideheuvel

The IPR-programme is performed by an interdisciplinary treatment team, consisting of a pulmonologist, psychologist, respiratory nurse, physiotherapist, exercise therapist, dietician,
social worker, therapeutic recreation specialist and occupational therapist. The main goals of the IPR-programme are reducing the impairment of daily functioning and prevention of deterioration and exacerbations. Because patients with severe chronic asthma often experience similar problems as patients with COPD, such as deconditioning and inadequate disease behaviour, the IPR programme is open to both types of patients. The standardized programme with individual adaptations consists of several clinical and psychosocial aspects [10,308]:

- an extensive diagnostic period focussing on both somatic and psychosocial problems and their interaction;
- optimisation of the medication regimen and decreasing the amount of oral corticosteroids; disease education (causes, pathophysiology, symptoms, treatment);
- education on medication and correct use of medication (total education time varying from 1 hour/week for all patients to 2-3 hours/week for patients needing extensive help with use of their medication);
- training of adequate disease behaviour and self-management skills;
- exacerbation management, including an individualized ‘what to do’ list to prevent exacerbations when lung function decreases or symptoms increase;
- extensive group-based and individual psychosocial counselling (1 to 4 hours/week);
- chest physiotherapy and breathing retraining;
- and exercise training with varying intensity depending on the individual tolerance: exercise training consists of diverse upper and lower extremity exercises, ranging from 3 times a week 30' interval training with low intensity ADL-related exercises for patients with very severe COPD, up to 5 times a week (45' to 60' each session) interval and endurance training with moderate to high intensity for patients with moderate severe asthma or COPD.

The duration of the IPR ranges from 3 to 6 months, depending on the specific problems and treatment goals of a patient. Because of the large variation in individual problems and the essential role of motivation in pulmonary rehabilitation [10], individualized treatment goals are formulated by the multidisciplinary treatment team in consultation with the patient. After the one-week multidisciplinary diagnostic phase, an extensive integrated description of the specific problems of the patient is made. Individualized treatment goals, based on this problem description, are formulated by the treatment team in consultation with the patient. These treatment goals are formulated in words familiar to the patient to ensure comprehension of content and maximal motivation. Examples of individual treatment goals can be found in chapter 7.
1.11 Research questions

The main reason for the outcomes research described in this thesis is the lack of systematically acquired knowledge about the outcome of inpatient pulmonary rehabilitation in patients with asthma or COPD. Therefore an observational study was done to describe the short- and long-term outcome of inpatient pulmonary rehabilitation, in patients with asthma or COPD referred to Asthmacenter Heideheuvel. In addition to this outcome study, several studies were designed to address some of the methodological problems with assessing outcome in inpatient pulmonary rehabilitation. The research questions addressed in this thesis are as follows:

I What are the short- and long-term outcomes of inpatient pulmonary rehabilitation in patients with asthma or COPD referred to Asthmacentre Heideheuvel;
A What are the short- and long-term clinical and physiological outcomes of inpatient pulmonary rehabilitation in patients with asthma or COPD (chapter 2);
B What are the short- and long-term outcomes on health status and psychosocial functioning of inpatient pulmonary rehabilitation in patients with asthma or COPD (chapter 3);
C How robust are the outcomes of inpatient pulmonary rehabilitation when missing data are imputed using sensitivity analysis? (chapter 4);

II Does the use of multiple factors add to walking distance in describing performance in the six minute walking test, a measure for functional exercise tolerance (chapter 5);

III What are the longitudinal measurement properties of the Quality of Life for Respiratory Illness Questionnaire (QoLRIQ), a health status questionnaire for patients with asthma or chronic obstructive pulmonary disease (chapter 6):
A Is the QoLRIQ sensitive to change and longitudinally valid;
B What is the size of a minimal important difference;
C What is the validity of retrospective computing of minimal important differences;

IV What is the outcome of inpatient pulmonary rehabilitation as measured by the subjective assessment by patients of attaining individualised treatment goals; and what are the sensitivity to change, reliability and longitudinal validity of that subjective assessment method (chapter 7).
1.12 Reference List


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