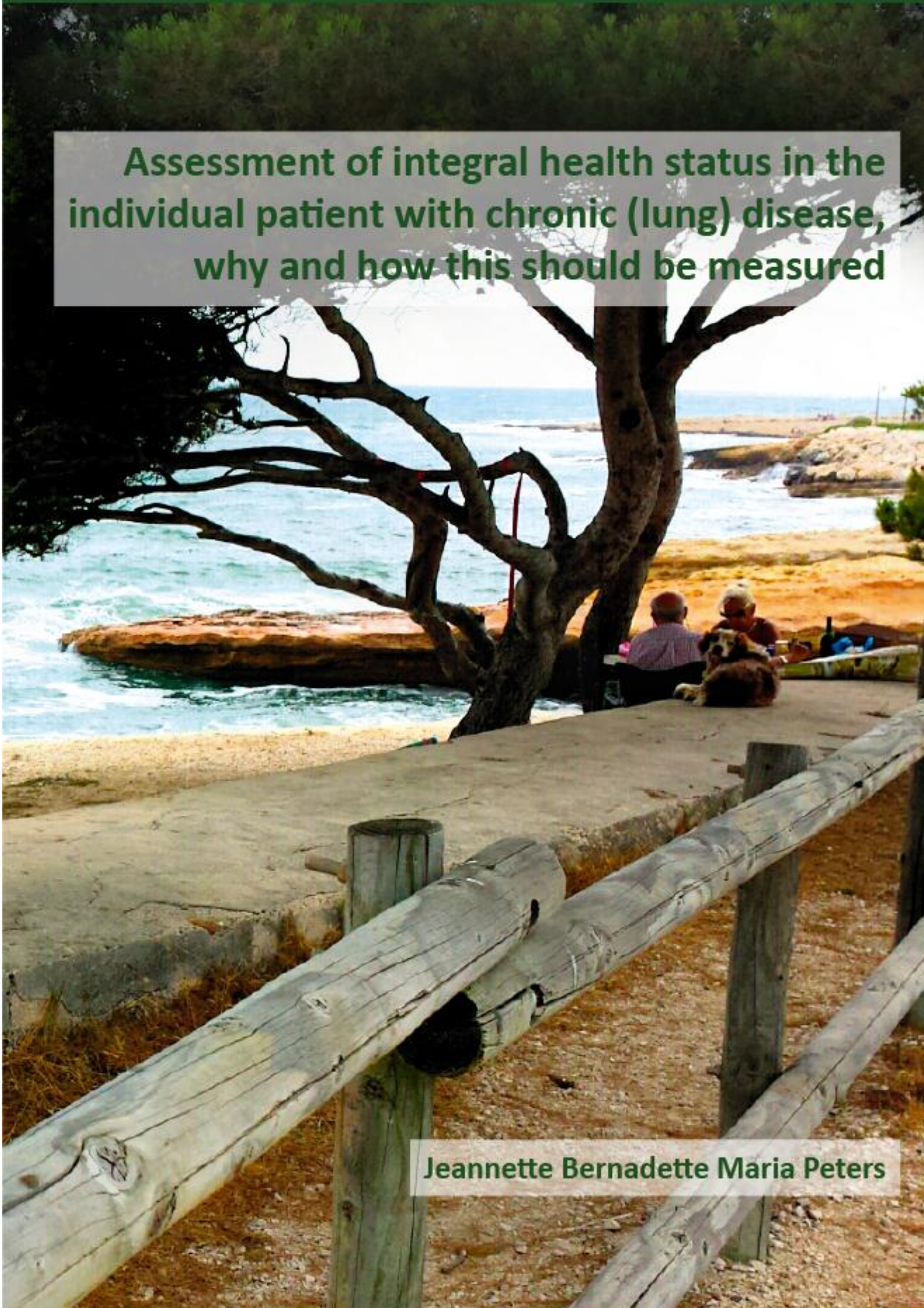
Assessment of integral health status in the individual patient with chronic (lung) disease, why and how this should be measured

Jacobs-Peters, J.B.M.

2015, Dissertation

Assessment of integral health status in the individual patient with chronic (lung) disease, why and how this should be measured



Jeannette Bernadette Maria Peters

Assessment of integral health status in the individual patient with chronic (lung) disease,

why and how this should be measured

Jeannette Bernadette Maria Peters

ISBN:
978-90-6464-833-5

Printed by:
GVO drukkers & vormgevers B.V. |Ponsen en Looijen

Cover:
Design: Ineke Jansen, GVO drukkers & vormgevers B.V.
Photo: J.B.M. Peters

Lay-out
J.B.M. Peters

Assessment of integral health status in the individual patient with chronic (lung) disease,

why and how this should be measured

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. Th.L.M. Engelen,
volgens besluit van het college van decanen
in het openbaar te verdedigen op dinsdag 27 januari 2015
om 14.30 uur precies

door
Jeannette Bernadette Maria Peters
geboren op 23 september 1975
te Boxmeer

Promotoren:

Prof. dr. J.B. Prins
Prof. dr. P.N.R. Dekhuijzen

Copromotoren:

Dr. J.H.M.M. Vercoulen
Dr. J. Molema
Dr. Y.F. Heijdra

Manuscriptcommissie:

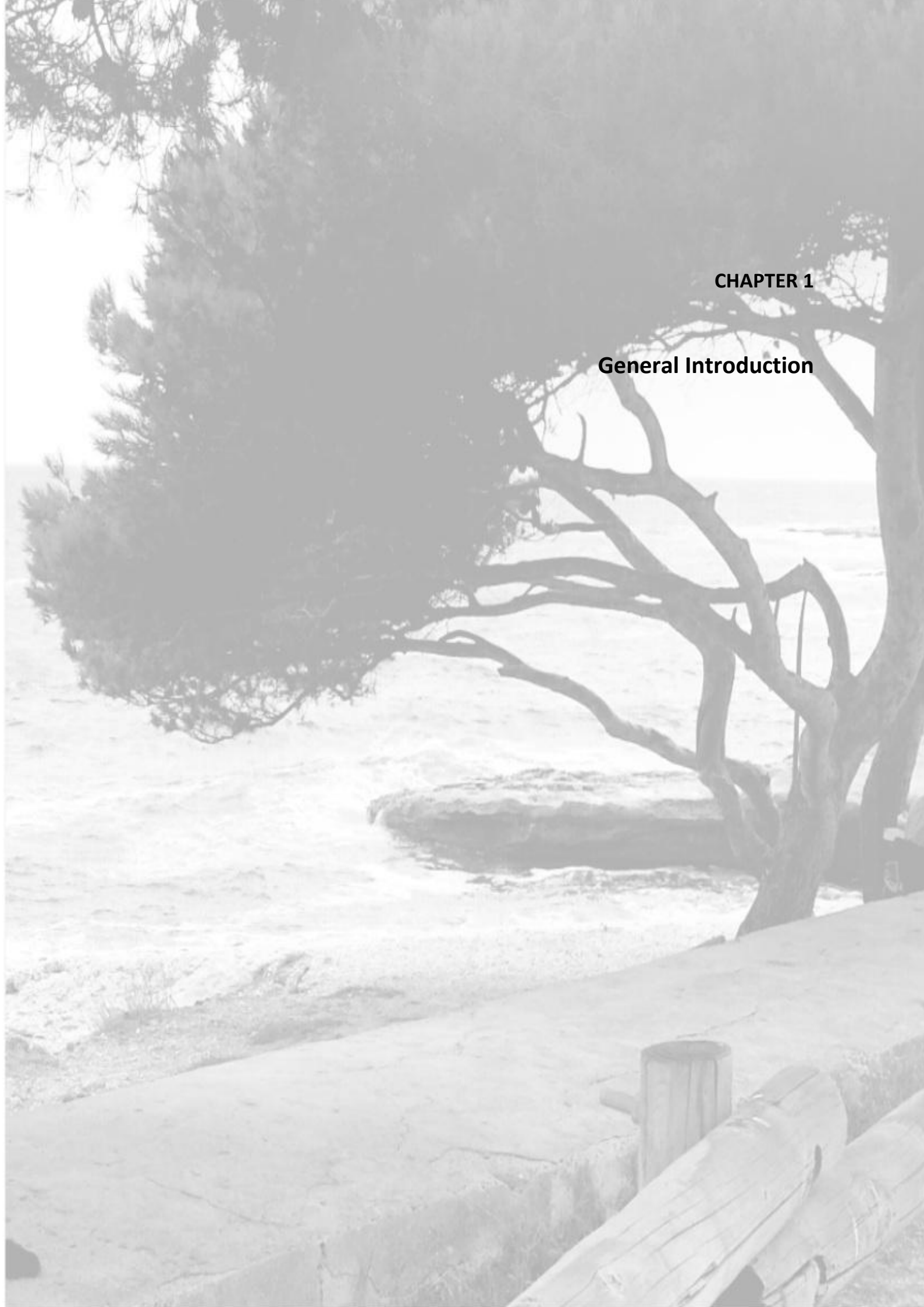
Prof. dr. W.J.J. Assendelft
Prof. dr. G.P. Westert
Prof. dr. R. Sanderman (UMCG)

Paranimfen:

Lonneke Boer
Penny Philips -Jansen

Content

If you change nothing, nothing will change



CHAPTER 1

General Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined by the Global Initiative for Chronic Obstructive Lung Diseases (GOLD) as 'a common preventable and treatable disease that is characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases' [1]. Exacerbations, comorbidities, and systemic effects are very common in COPD [1, 2]. A clinical diagnosis of COPD should be considered when a patient presents with dyspnea, chronic cough, sputum production and/or wheezing, and a history of exposure to risk factors [1, 2]. The main risk factor for COPD is tobacco smoking and to a lesser extent indoor air pollution, dust and chemicals, and outdoor air pollution [1]. The diagnosis of COPD is confirmed if there is persistent airflow limitation, defined as a post-bronchodilator FEV_1/FVC ratio <0.70 [1]. On the basis of the post-bronchodilator FEV_1 percentage of predicted, the severity of airflow limitation is defined as mild, moderate, severe, or very severe (Table 1).

Table 1 Characterization of severity of airflow limitation in COPD

	Characteristics
I. Mild	$FEV_1 \geq 80\%$ of predicted
	$FEV_1/FVC < 70\%$
II. Moderate	$FEV_1 \leq 80\%$ and $FEV_1 \geq 50\%$ of predicted
	$FEV_1/FVC < 70\%$
III. Severe	$FEV_1 \leq 50\%$ and $FEV_1 \geq 30\%$ of predicted
	$FEV_1/FVC < 70\%$
IV. Very severe	$FEV_1 \leq 30\%$ predicted
	$FEV_1/FVC < 70\%$

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity [1]

The estimated prevalence of COPD in 2000 was 210 million people worldwide [3]. COPD is currently the fifth leading cause of death and it is estimated that it will be the fourth leading cause of death worldwide in 2030 [4]. In the Netherlands, approximately 2.4% of men and 1.7% of women are diagnosed with COPD [5]. These percentages are probably an underestimation, because COPD is typically not diagnosed before it is clinically apparent and moderately advanced. One reason for the late diagnosis is that COPD is a chronic, progressive disease. It develops slowly, and patients tend to attribute symptoms or decreased exercise tolerance to aging [6]. In general, patients do not consult their general practitioner until they experience symptoms and/or are confronted by variability in lung function that affects their daily life [7] and not for the presence of respiratory symptoms or a (gradually) reduced lung function. Another possible reason for the late diagnosis in the Netherlands is that case-finding is not standard, and screening is recommended only for

those patients who are (ex-) smokers, who are older than 40 years with chronic cough and/or use of inhaled medication, or who had >2 infections of the lower airways in the past year [5]. Once a patient is diagnosed with COPD, treatment can be started. The majority of patients with COPD are treated by their general practitioner in primary care, with the exception of patients who do not respond to treatment, who have an unclear diagnosis, who are hospitalized, or who have advanced disease. These patients are generally referred to a pulmonologist in secondary care. The focus of treatment is mainly on controlling the disease, to improve physiological functioning. However, from the patient's point of view, treatment should be aimed at the illness, at reducing fatigue, dyspnea, and impairments. Current guidelines integrate these aims: 'treatment of COPD is aimed at reducing the impact of the symptoms and long term lung function decline, as well as prevention of future exacerbations, improvement of exercise tolerance and health status' [1, 2]. Treatment is with pharmacological (i.e., bronchodilators, corticosteroids, vaccines, antibiotics) and/or non-pharmacological (pulmonary rehabilitation, oxygen therapy, surgical treatment, smoking cessation, physical activity, education, self-management) interventions.

Unfortunately, as some of the consequences of COPD are permanent, because of the chronic and progressive nature of the disease, patients must adapt by changing their behavior. This not only diminishes perceived fatigue, dyspnea, and impairments but also has a positive effect on disease progression. Although the ultimate goal of treatment is the same for all patients, the way this goal is achieved is different for each patient. COPD is a very heterogeneous disease not only with respect to its different physiological manifestations but also with respect to how individual patients perceive the disease and its side effects. Everybody interprets a given situation in their own way, depending on their somatic, cognitive emotional, behavioral, and social appraisal. These aspects cannot be neglected when treating a chronic disease.

Indeed, there has been a shift in guidelines on the diagnosis and treatment of COPD – from focusing exclusively on treatment of the disease to focusing on treatment of the illness, which encompasses not only disease management but also the somatic, cognitive emotional, behavioral, and social effects on the patient. In the past, treatment was guided (solely) by the severity of the airflow limitation [8, 9], but nowadays treatment is guided by disease severity, a combination of airflow limitation, health status, and risk of future events (such as exacerbations and hospital admissions) [1, 2]. This is completely in line with the change from the biomedical model to the biopsychosocial model for the treatment of chronic disease.

In the past, the body and mind were seen as separate entities, with 'illness of the body' being treated by medical doctors, guided by measurable biological and physiological variables, and 'illness of the mind' being treated by psychiatrists/ psychologists, guided by the psychological and social context. For many years, these two fields existed alongside each other, both neglecting the relations that exist between the biological, psychological, and social dimensions of health in the patient. In 1977 Engel [10] introduced a blueprint for the biopsychosocial model for the treatment of disease, to replace the inadequate biomedical model in medicine. Whereas with the biomedical model treatment is guided solely by

measurable biological variables, the biopsychosocial model incorporates psychological, social, and behavioral dimensions of disease. Engel stated that all three dimensions (biological, psychological, and social) have a unique influence on the development, progression, and experience of disease, and thus should be measured to provide adequate treatment.

From this point of view, numerous studies have investigated the impact of disease on patients, expressed in terms of quality of life, health-related quality of life, and health status. These concepts are often used interchangeably, which has led to conceptual confusion in the literature. Some definitions of these concepts are based on the definition of the World Health Organization, which defines health as 'a state of complete physical, mental, and social well being, and not merely the absence of disease or infirmity' [11]. Although all three concepts are used to investigate a patient's health, they have a different focus. Both quality of life and health status measure the same domains (biological, psychological, and social), but at a different level, namely, only subjectively versus also objectively, respectively [12, 13]. Moreover, quality of life is defined as 'how satisfied a person is with life' in the biological, psychological, and social domains [12-17], and health-related quality of life as satisfaction with health (physiological functioning) [18]. Health status measures the same aspects, but also focuses on the objective impact of the disease [12, 13] and not solely on the patient's satisfaction. It is important to know the real (objective) and perceived (subjective) impact of disease on a patient's health to get a clear picture.

The conceptual model of health status of Wilson and Cleary [19] includes both the objective and subjective evaluation of the impact of disease on diverse dimensions. In line with the biopsychosocial view, their model includes the following domains: biological and physiological processes, and the perception of symptoms, functioning, general health, and overall quality of life (Figure 1). This model is not a causal model in which one aspect leads to the other, but is a phenomenological model. It includes several dimensions that all have a unique place and are at best moderately related.

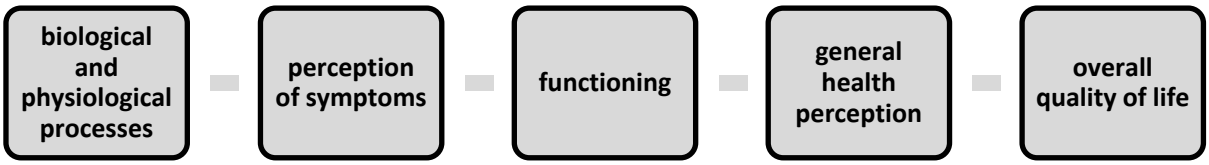


Figure 1 Conceptual model of health status developed by Wilson and Cleary [19]

In line with this model, our research group developed the Nijmegen Integral Assessment Framework (NIAF) [20] to measure a person's integral health status. On the basis of theoretical models and clinical considerations, we defined concepts and then empirically tested these concepts with relevant tests and instruments in 168 outpatients. Factor analysis revealed that integral health status compromises at least four main domains: physiological functioning, symptoms, functional impairment, and quality of life, each of

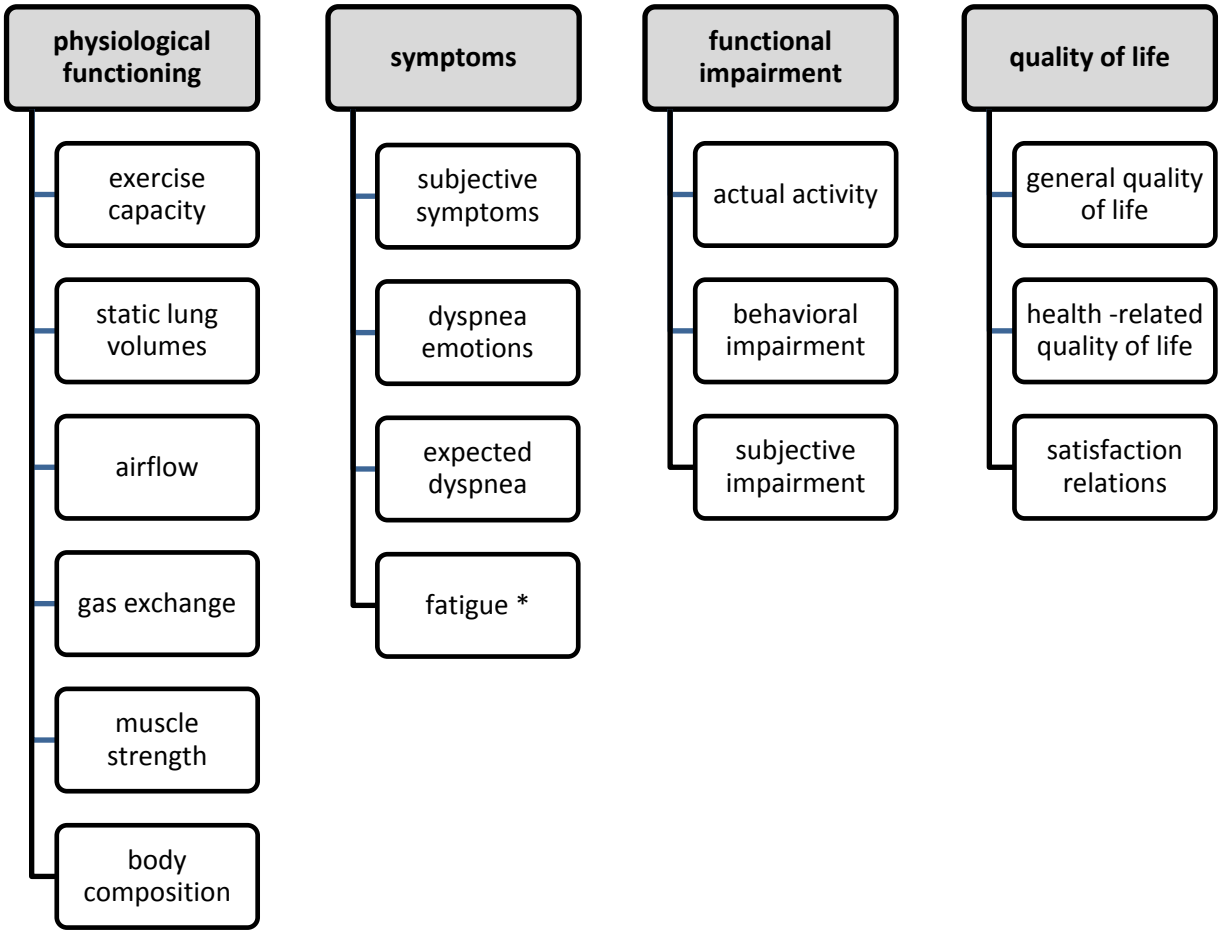


Figure 2 The Nijmegen Integral Assessment Framework (NIAF): A conceptual model of integral health status in patients with Chronic Obstructive Pulmonary Disease developed by Vercoulen et al. [20] *Note: *added as subdomain in 2010*

which can be subdivided into many sub-domains (see Figure 2 and Table 1). There were low-to-moderate correlations between the sub-domains, indicating that all sub-domains measure unique aspects of health status. Since these sub-domains are relatively unrelated, all sub-domains need to be measured in order to gain a complete picture of a patient's integral health status.

The various instruments developed to describe the impact of disease on a patient can be broadly divided into disease-specific and generic questionnaires. They both have their strengths and weaknesses. Whereas disease-specific instruments have a narrow focus and are often centered on the core symptoms of the disease, generic instruments cover universal symptoms and have a broader focus, which makes it possible to compare the impact on health status between different diseases. Frequently used disease-specific instruments in COPD are the St George Respiratory Questionnaire (SGRQ) [26], the Quality of Life Respiratory Illness Questionnaire (Qol-RiQ) [27], the Clinical COPD Questionnaire (CCQ) [28], and the COPD Assessment Test (CAT) [29]. The Short Form 36 (SF-36) [30] and the Sickness Impact Profile (SIP) [22] are two generic instruments frequently used in COPD research.

These instruments measure general symptoms, activity limitations, and/or emotions, and are typically used to describe the impact of disease in patient populations and the effects of interventions at a group level. These instruments have proven their merit in a research setting but are less useful in a clinical setting, because the questionnaires are long, time-consuming or difficult to score, and often lack reference values, which makes it difficult to interpret findings; moreover, some instruments measure only limited aspects of health. As the domains of health status are only moderately related, it is essential to measure all domains in order to get a complete picture of the patient [20, 31-32]. Only then is tailored treatment possible, which is necessary because usual care is often insufficiently effective.

Aim and outline of the thesis

COPD is a chronic progressive disease that influences patients' integral health status. Guidelines recommend that treatment be guided by disease severity, a composite of severity of airflow limitation, risk of future exacerbations, and impact on health status. There is, therefore, a need for an instrument that measures the various aspects of integral health status and which is easy to use and interpret and which can be completed within a limited time. The studies described in the chapters of this thesis focus on the measurement of integral health status – on the development of a relevant instrument for patients with COPD, its application in clinical care, and its usefulness for other chronic diseases. The Nijmegen Integral Assessment Framework (NIAF) can be used to guide the measurement of integral health status [20]. It covers the four main domains physiological functioning, symptoms, functional impairment, and quality of life, subdivided into 15 unique and relatively unrelated sub-domains (Figure 2, Table 2).

Chapter 2 focuses on fatigue. Although fatigue is the second most reported symptom in COPD [33-36], there has been little research interest in the role of fatigue in COPD or its possible association with aspects of integral health status. As the NIAF also did not incorporate fatigue, the study described in this chapter investigates the prevalence, severity, and natural course of fatigue in patients with COPD, and the association between fatigue and the sub-domains of integral health status.

Chapter 3 describes the development of a short version of the NIAF that can be used in a clinical setting: the Nijmegen Clinical Screening Instrument (NCSI). The NIAF contains many tests and instruments, which make it time-consuming to administer, score, and interpret. Moreover, there are no cut-off scores to determine whether scores are normal or abnormal. These aspects are essential for an instrument to be used in clinical practice.

In *Chapter 4,* the NIAF is compared with the St George Respiratory Questionnaire (SGRQ), a disease-specific instrument frequently used to investigate COPD populations. The SGRQ has been used widely to measure health status, but as it contains only three subscales (symptoms, activity, impacts) and a total score, it can be questioned whether it covers all aspects of health status.

Table 2 Main domains and sub-domains of the Nijmegen Integral Assessment Framework (NIAF), their definition and corresponding instruments, subscales/measurement

Main domain	Sub-domain	Definition	**Instrument**: subscale/measurement
Physiological Functioning	Exercise Capacity		**V_{max} 29, Sensor Medics**: VO_2 maximum% predicted Heart rate maximum% predicted TLCO % predicted BE delta
	Static Lung Volumes		**Masterscreen PFT spirometer/ diffusion, Jaeger** : TLC % predicted RV % predicted
	Airflow		**Masterscreen PFT spirometer/ diffusion, Jaeger**: Post-bronchodilator FEV_1% predicted MEF50 % predicted VE % predicted
	Gas Exchange		**V_{max} 29, Sensor Medics**: Delta (A-a)DO2 (kPa) **V_{max} 29, Sensor Medics** Delta PaCO2 (kPa)
	Muscle Strength		**Validyne CD23**: PE_{max}% predicted **Validyne CD23**: PI_{max} % predicted Quadriceps % predicted
	Body Composition		BMI **Bodystat**: FFMI
Symptoms	Subjective Symptoms	The patient's overall burden of pulmonary symptoms	**PARS-D [20]**: Global Dyspnea Activity **PARS-D [20]**: Dyspnea Activity **PARS-D[20]**: Global Dyspnea Burden **QoL-RIQ [21]**: Breathing Problems
	Dyspnea Emotions	The level of frustration, depressive feelings, and anxiety a patient experiences when dyspnoeic	**DEQ [20]**: Mood **DEQ[20]**: Frustration **DEQ[20]**: Anxiety
	Expected Dyspnea	The level of dyspnea a patient expects to experience during specific activities no longer performed	**PARS-D [20]**: Expected Dyspnea
Functional Impairment	Actual Activity	The actual physical activity a patient performs during two weeks	**Accelerometer**: Mean
	Behavioral Impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	**SIP [22]**: Home Management **SIP [22]**: Ambulation **SIP [22]**: Body Care & Movement **SIP [22]**: Mobility
	Subjective Impairment	The experienced degree of impairment in general, and in social functioning	**QoL-RIQ [21]**: General Activities **QoL-RIQ [21]**: Social Activities Global impairment[19] **SIP [22]**: Social Interaction **SIP [22]**: Burden
Quality of Life	General QoL	Mood, anxiety, and the satisfaction of a person with his/her life as a whole	**BDI [23]**: Primary Care **SWLS [24]**:Total **SCL [25]**: Anxiety
	HRQol	Satisfaction related to physiological functioning and the future	Satisfaction Physical [20] Satisfaction Future [20]
	Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction Spouse [20] Satisfaction Social [20]

Chapter 5 describes the identification of clinical phenotypes based on health status. These clinical phenotypes reflect adaptation to the disease. To date, phenotypes have been identified mainly on the basis of different underlying pathophysiological mechanisms. In contrast, in this study the focus is on behavioral aspects and whether there are differences (changes in integral health status) between these clinical phenotypes in their response to care as usual and to inpatient pulmonary rehabilitation.

To examine whether the NCSI can also be used for patients with other diseases, two studies investigate its use in a group of patients with asthma (C*hapter 6)* and in a group of patients with Q-fever (C*hapter 7)*. As the NCSI consists of disease-specific and generic subscales, it can theoretically be used in these patients because they have similar symptoms. In addition to the NCSI, the usefulness of other questionnaires, such as the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ), is also investigated in patients with asthma. Lastly, the general findings and implications for clinical practice and future research are presented in Chapter 8.

Abbreviations used in table 2:

% predicted, percentage of predicted value; BDI, Beck Depression Inventory**;** BE, Base Excess; BMI, Body Mass Index; DEQ, Dyspnea Emotions Questionnaire; FEV_1, Forced Expiratory Volume in one second postbronchodilator value; FFMI, Fat Free Mass Index; MEF50, mid-expiratory Flow at 50% of forced vital capacity; PARS-D, Physical Activity Rating Scale –Dyspnea; PI_{max}, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; QoL-RIQ, Quality of Life for Respiratory Illness Questionnaire; RV, Residual Volume; TLC, Total Lung Capacity; TLCO, transfer capacity (of lung) for carbon monoxide; SCL, Symptom Checklist; SIP, Sickness Impact Profile; SWLS, Satisfaction With Life Scale; VE, minute ventilation ;VO_2max, maximal oxygen uptake.

REFERENCES

1. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. Available from: http://www.goldcopd.org/
2. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the COPD Patient. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. Proceedings of the Americain Thoracic Society. 2012: 9(1):9-18.
3. World Health Organization. Global surveillance, prevention and control of chronic respiratory diseases: A comprehensive approach. In: WHO, ed., 2007; p. 155.
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006: 3(11):e442.
5. Nederland Long Alliantie Nederland. Zorgstandaard COPD 2010.
6. van Schayck CP, Chavannes NH. Detection of asthma and chronic obstructive pulmonary disease in primary care. European Respiratory Journal Supplement. 2003: 39:16s-22s.

7. van den Boom G, Rutten-van Molken MP, Tirimanna PR, van Schayck CP, Folgering H, van Weel C. Association between health-related quality of life and consultation for respiratory symptoms: results from the DIMCA programme. European Respiratory Journal. 1998: 11(1):67-72.
8. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. European Respiratory Journal. 2004: 23(6):932-946.
9. Global Initiative for Chronic Obstructive Lung Disease. Workshop Report: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - 2005 Update. 2005
10. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977: 196(4286):129-136.
11. World Health Organization. The first ten years of the World Health Organization. Geneva: World Health Organization,1958.
12. Fayed N, Schiariti V, Bostan C, Cieza A, Klassen A. Health status and QOL instruments used in childhood cancer research: deciphering conceptual content using World Health Organization definitions. Quality of Life Research. 2011: 20(8):1247-1258.
13. Smith KW, Avis NE, Assmann SF. Distinguishing between quality of life and health status in quality of life research: a meta-analysis. Quality of Life Research 1999: 8(5):447-459.
14. Cohen SR, Mount BM, MacDonald N. Defining quality of life. European journal of cancer. 1996: 32A(5):753-754.
15. Ferrans CE. Conceptualizations of quality of life in cardiovascular research. Progress in cardiovascular nursing. 1992: 7(1):2-6.
16. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. International journal of nursing studies. 2006: 43(7):891-901.
17. Haas BK. A multidisciplinary concept analysis of quality of life. Western journal of nursing research. 1999: 21(6):728-742.
18. Taylor RM, Gibson F, Franck LS. A concept analysis of health-related quality of life in young people with chronic illness. Journal of clinical nursing. 2008: 17(14):1823-1833.
19. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Journal of the Americain Medical Association 1995: 273(1):59-65.
20. Vercoulen J, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavioural Medicine. 2008: 15(4):263-279.
21. Maille AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA. The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QOL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91(5):297-309.
22. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical Care. 1981: 19(8):787-805.
23. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behavioural and Research Therapy. 1997: 35(8):785-791.
24. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. Journal of Personality Assessment. 1985: 49(1):71-75.

25. Arrindell WA, Ettema JHM. SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator [SCL-90: Manual for a multifaceted measure of psychopathology]. Swets & Zeitlinger, Lisse, 1986.
26. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory medicine 1991: 85 Suppl B: 25-31;discussion 33-27.
27. Maille AR, Kaptein AA, Koning CJ, Zwinderman AH. Developing a quality-of-life questionnaire for patients with respiratory illness. Monaldi Archives for Chest Disease. 1994: 49(1):76-78.
28. Van Der Molen T, Willemse BW, Schokker S, Ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and Quality of Life Outcomes. 2003: 1(1):13.
29. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline LN. Development and first validation of the COPD Assessment Test. European Respiratory Journal 2009: 34(3):648-654.
30. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992: 30(6):473-483.
31. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, Tal-Singer R, Wouters E, Yates JC, Vestbo J. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respiratory Research. 2010: 11:122.
32. Verhage TL, Vercoulen JH, van Helvoort HA, Peters JB, Molema J, Dekhuijzen PN, Heijdra YF. Maximal exercise capacity in chronic obstructive pulmonary disease: a limited indicator of the health status. Respiration; international review of thoracic diseases. 2010: 80(6):453-462
33. Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. Journal of Pain and Symptom Management. 2009: 38(1):115-123.
34. Gift AG, Shepard CE. Fatigue and other symptoms in patients with chronic obstructive pulmonary disease: do women and men differ? Journal of Obstetric Gynecologic and Neonatal Nursing. 1999: 28(2):201-208.
35. Guyatt GH, Townsend M, Berman LB, Pugsley SO. Quality of life in patients with chronic airflow limitation. British Journal of Diseases of the Chest. 1987: 81(1):45-54.
36. Walke LM, Byers AL, Tinetti ME, Dubin JA, McCorkle R, Fried TR. Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure. Archives of Internal Medicine. 2007: 167(22):2503-2508.

CHAPTER 2

Course of normal and abnormal fatigue in patients with Chronic Obstructive Pulmonary Disease, and its relationship with domains of health status

Jeannette B Peters
Yvonne F Heijdra
Leonie Daudey
Lonneke M Boer
Johan Molema
P N Richard Dekhuijzen
Tjard R Schermer
Jan H Vercoulen

Patient Education and Counseling. 2011: 85(2):281-285

ABSTRACT

Objective

To examine the difference between patients with normal and patients with abnormal fatigue on aspects of health status, and investigate the natural course of fatigue in patients with Chronic Obstructive Pulmonary Disease (COPD).

Methods

Fatigue, physiological functioning, functional impairment, symptoms, and Quality of Life (QoL) were measured in 168 patients with COPD, and longitudinal data on fatigue of 77 patients were collected.

Results

Fifty percent of patients had abnormal fatigue. Patients with abnormal fatigue reported significantly more problems on the sub-domains of functional impairment (except actual physical activity), symptoms, and QoL as compared to patients with normal fatigue. With respect to physiological functioning patients with normal fatigue scores had better exercise capacity. Four years later the percentage of patients with abnormal fatigue was increased to 64%. In 1/3 of the patients an increase of more than the minimal clinically important difference was found.

Conclusions

Many COPD patients suffer from abnormal fatigue. Patients with abnormal fatigue have more limitations on many aspects of health status, especially on symptoms, functional impairment, and QoL.

Practice implication

Fatigue should be evaluated in usual care with a questionnaire that corrects for normal fatigue in order to tailor treatment to patients' needs.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and disabling disease, which is accompanied by a variety of symptoms. In guidelines, dyspnea, cough, and sputum production are marked as key symptoms of COPD [1]. Although not marked as a key symptom, fatigue was reported by patients with COPD as the second most important symptom of COPD, after dyspnea [2-4].

Of patients with severe COPD 47-58% reported to experience fatigue every day or several days a week [5,6]. Patients described their fatigue as a feeling of general tiredness [7] and as 'feeling drained of energy' [8]. In addition, they reported that the experienced fatigue put restrictions upon their lives and made them dependent upon others [8]. Patients also reported that the feeling of fatigue was irritating, frustrating [7], and interfered with their ability to concentrate [9].

In the past years, several empirical studies have been performed in which fatigue was merely used as an outcome measure of an intervention [10-13]. Relatively few studies have studied the relationships between fatigue and many aspects of health status. Some studies showed fatigue to be significantly related to impaired postbronchodilator forced expiratory volume in one second (FEV_1) [14], reduction in exercise capacity [14], and more problems in Quality of Life (QoL) [14,15]. Moderate, but significant, correlations were found between fatigue on the one hand and anxiety [16] and depression [15,16] on the other. Correlations of 0.32 to 0.69 between fatigue and dyspnea have been reported [5,15,17,18]. Other studies did not find significant relationships between fatigue and exercise capacity [16,19], or FEV_1 [15,16,19-21].

Studies on the natural course of severity of fatigue in patients with COPD using standardized measures are lacking. Besides the fact that fatigue is a highly non-specific symptom and a key symptom in many psychiatric and somatic diseases, fatigue is also a normal phenomenon that healthy persons experience as well. Hence, in determining the severity of fatigue a correction for normal fatigue has to be made.

The aims of the present study are to investigate the prevalence of 'normal' and 'abnormal' fatigue, and the relationship between fatigue and health status in patients with COPD. In addition, we investigated the natural course of fatigue in COPD.

METHODS

Participants

One-hundred-sixty-eight COPD patients were recruited from three different pulmonary outpatient clinics in the Netherlands, between May 2002 and May 2003. All patients were diagnosed with COPD [1]. Exclusion criteria were an acute exacerbation, recent (<6 months) participation in pulmonary rehabilitation program, primary comorbidity that may dominate health status, inability to speak or read Dutch, and inability to completely adhere to the

Table 1 Main domains and sub-domains of the Nijmegen Integral Assessment Framework (NIAF) and their corresponding instruments, subscales.

Main domain	Sub-domain	Instrument Subscale/ Measurement
Physiological Functioning	Exercise Capacity	VO_2 maximum% predicted[a]
		Heart rate maximum% predicted[a]
		TLCO% predicted[a]
		BE delta[a]
	Static Lung Volumes	TLC% predicted[b]
		RV% predicted[b]
	Airflow	Post-bronchodilator FEV_1% predicted[b]
		MEF50% predicted[b]
		VE% predicted[b]
	Muscle Strength	PE_{max}% predicted[c]
		PI_{max} % predicted[c]
		Quadriceps% predicted[c]
	Body Composition	BMI[d]
		FFMI[d]
Symptoms	Subjective Symptoms	PARS-D Global Dyspnea Activity [22]
		PARS-D Dyspnea Activity [22]
		PARS-D Global Dyspnea Burden [22]
		QoL-RIQ Breathing Problems [29]
	Dyspnea Emotions	DEQ-Mood [22]
		DEQ-Frustration [22]
		DEQ-Anxiety [22]
	Expected Dyspnea	PARS-D Expected Dyspnea [22]
Functional Impairment	Actual Physical Activity	Aktometer Mean [31,32]
	Behavioral Impairment	SIP Home Management [30]
		SIP Ambulation [30]
		SIP Body Care & Movement [30]
		SIP Mobility [30]
	Subjective Impairment	QoL-RIQ General Activities [29]
		QoL-RIQ Social Activities [29]
		Global impairment [22]
		SIP Social Interaction [30]
		SIP Burden [30]
Quality of Life	General QoL	BDI Primary Care [34]
		SWLS-Total [35]
		SCL Anxiety [33]
	HRQoL	Satisfaction Physical [22]
		Satisfaction Future [22]
	Satisfaction Relations	Satisfaction Spouse [22]
		Satisfaction Social [22]

Note: Instruments used: [a]=Vmax 29, Sensor Medics ; [b]=Masterscreen PFT spirometer / diffusion, Jaeger, [c]=Validyne CD23, [d]=W/H^2, Bodystat. *Abbreviations:* %, percentage of predicted ; BDI, Beck Depression Inventory**;** BE, Base Excess; BMI, Body Mass Index; DEQ, Dyspnea Emotions Questionnaire; FEV_1, Forced Expiratory Volume in one second postbronchodilator value; FFMI, Fat Free Mass Index; MEF50, mid-expiratory Flow at 50% of forced vital capacity; PARS-D, Physical Activity Rating Scale –Dyspnea; PImax, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; QoL, Quality of Life; HrQoL, health related quality of life; QoL-RIQ, Quality of Life for Respiratory Illness Questionnaire; RV, Residual Volume; TLC, Total Lung Capacity; TLCO, transfer capacity (of lung) for carbon monoxide; SCL, Symptom Checklist; SIP, Sickness Impact Profile; SWLS, Satisfaction With Life Scale; VE, minute ventilation ;VO_{2max}, maximal oxygen uptake.

research protocol. A detailed description of the recruitment procedure and the study sample can be found elsewhere [22]. Four years later patients were asked to participate in a follow-up study. Patients gave informed consent and the local Ethics Committee approved both studies.

Outcome variables

Fatigue was measured by the Subjective Fatigue subscale of the Checklist Individual Strength (CIS) [23], a standardized and validated questionnaire that has been used in cohorts of healthy subjects [24,25], and in various patient populations [23,26,27]. The subscale consists of 8 items, scored on a seven point Likert-scale. Based on the total score, three subgroups can be defined: normal fatigue (≤26), mild fatigue (27-35) or severe fatigue (≥36). In this study we used two categories in the analyses: normal and abnormal fatigue. Abnormal fatigue was defined as either mild or severe fatigue. The minimally clinically important difference (MCID) is 10 points.

Health status was measured by the Nijmegen Integral Assessment Framework (NIAF) [22], which covers four main domains: physiological functioning, symptoms, functional impairment, and QoL. These main domains were shown to be subdivided into 15 sub-domains each representing a unique aspect of the patient's health status. The NIAF organizes existing tests and instruments according to the sub-domains they measure (Table 1). A sub-domain total score was calculated for each sub-domain.

Statistical analysis

Mann-Whitney U tests were performed to study the differences between patients with normal and patients with abnormal fatigue on the sub-domains of health status. Paired *t*-tests were performed to test significant changes between the baseline and follow-up measurements. The *p*-value was set at <0.01. All analyses were performed using SPSS 14.0

RESULTS

Table 2 shows characteristics of the COPD patients at baseline.

Abnormal fatigue and relationships between fatigue and health status

At baseline, half of the 168 COPD patients experienced abnormal fatigue (mild plus severe), and a quarter experienced severe fatigue (Table 3). Significant relationships were found between fatigue and sub-domains of the main domains symptoms, functional impairment, and QoL (except actual physical activity). Patients with abnormal fatigue had significantly more problems on the sub-domains of the main domains symptoms, functional impairment and QoL (Table 4). The only exception was the actual physical activity sub-domain (as measured by an accelerometer), on which patients with or without abnormal fatigue

showed similar activity levels. On the main domain physiological functioning patients with abnormal fatigue scores only had significantly lower exercise capacity.

Table 2 Characteristics of COPD patients at baseline (N=168)

	Mean	±SD	[95% CI]
Age	64.5	±9.1	[63.1-65.9]
FEV_1% predicted	51.6	±13.6	[49.5-53.6]
FEV_1 (Liter)	1.52	±0.48	[1.44-1.59]
FEV_1/FVC%	43.6	±11.3	[41.2-44.7]
TLC% predicted	103.0	±16.0	[100.6-105.5]
RV% predicted	129.9	±35.8	[124.4-135.3]
TLCO% predicted	68.7	±23.9	[65.1-72.3]
BMI	25.6	±4.1	[25.0-26.2]
	n	(%)	
Gender (male/female)	131/37	(78/22%)	
GOLD			
Stage 1	0	(0%)	
Stage 2	88	(52.4%)	
Stage 3	80	(47.6%)	
Stage 4	0	(0%)	
Education			
Low	85	(52.2%)	
Middle	48	(29.4%)	
High	30	(18.4%)	
Personal Situation			
Partner	137	(84.0%)	
Divorced	7	(4.3%)	
Widowhood	11	(6.7%)	
Single	8	(4.9%)	

Abbreviations: FEV_1, Forced Expiratory Volume in one second postbronchodilator value; FEV_1 %predicted, FEV_1 postbronchodilator value as percentage of predicted value; FVC, Forced Vital Capacity; TLC, Total Lung Capacity; RV, Residual Volume; TLCO, transfer capacity (of lung) for carbon monoxide; BMI, Body Mass Index

Table 3 Mean (SD) and distribution of fatigue (CIS-Subjective Fatigue score) at baseline (N=168)

	Mean	±SD	[95% CI]
Group	27.3	±11.4	[25.5-29.0]
Fatigue, *n* (%)			
normal (≤ 26 points)	88	(52.4%)	
mild (≥ 27to ≤35 points)	39	(23.2%)	
severe (≥36 points)	41	(24.4%)	

Table 4 Correlations between fatigue and health status[a] and differences between COPD patients with normal and patients with abnormal fatigue on health status at baseline

	Pearson correlation with fatigue	Normal Fatigue (N=88) Mean	±SD	Abnormal Fatigue (N=78) Mean	±SD	p
Physiological Functioning						
Exercise Capacity	0.30#	445.5	±47.2	471.8	±35.7	<0.001
Static Lung Volumes	-0.06	152.2	±26.3	151.1	±31.5	n.s.
Airflow	0.07	782.5	±37.7	790.8	±35.9	n.s.
Muscle Strength	0.17	203.7	±30.3	213.4	±37.1	n.s.
Body Composition	0.04	864.9	±26.5	871.2	±30.3	n.s.
Symptoms						
Subjective Symptoms	0.60#	34.5	±12.4	50.7	±14.9	<0.001
Dyspnea Emotions	0.29#	13.7	±4.5	15.6	±4.8	0.003
Expected Dyspnea	0.34#	1.8	±0.8	2.7	±1.0	<0.010
Functional Impairment						
Actual Physical Activity	0.21	175.6	±29.5	184.7	±26.2	n.s.
Behavioral Impairment	0.46#	18.9	±14.0	30.8	±16.2	<0.001
Subjective Impairment	0.59#	44.2	±16.1	64.6	±18.5	<0.001
Quality of Life						
General QoL	0.51#	51.7	±9.5	63.6	±12.5	<0.001
HRQoL	0.55#	17.7	±6.8	25.3	±9.1	<0.001
Satisfaction Relations	0.37#	7.8	±7.6	12.3	±9.2	0.001

[a] For all sub-domains, the higher the score the more problematic; * p<0.01; n.s., non significant (p>0.01)

Course of fatigue in COPD patients (N=77): baseline vs. four years later

Forty-six percent of patients agreed to participate in the follow-up study after four years, reasons for non participation were diverse. No significant differences were found between patients who did not want to participate (91 patients) and patients who participated in the follow-up study (77 patients) with respect to age (mean 65.9 ±9.4 vs. 62.8 ±8.6; p=0.017), FEV_1% of predicted (mean 50.4 ±13.4 vs. 52.9 ±13.8; p=0.293), severity of fatigue (mean 28.0 ±11.6 vs. 26.5 ±11.2; p=0.463), or any of the health status sub-domains measured at baseline. For patients who had both assessments, FEV_1% predicted was not significantly different between baseline and after four years (p=0.200, Table 5).

After 4 years, mean fatigue scores were significantly higher compared to baseline (Table 5). The percentage of patients with abnormal fatigue (mild plus severe) increased. Worsening of fatigue with the MCID was found in 33% of the patients, and 12% of the patients had better scores after 4 years.

DISCUSSION & CONCLUSIONS

In the present study, we measured the severity and natural course of fatigue with a standardized questionnaire that corrects for normal fatigue in patients with stable moderate

to severe COPD. At baseline, almost half of the patients showed abnormal fatigue: 23% mild and 24% severe fatigue. Patients with abnormal fatigue had significantly more limitations in many sub-domains of quality of life, symptoms, and functional impairment than patients with normal fatigue. With respect to physiological functioning patients with abnormal fatigue had lower exercise capacity as compared to patients with normal fatigue. After 4 years, fatigue scores have become clinically relevant higher in one-third of patients, and clinically relevant lower in 12%.

DISCUSSION

Dyspnea is considered a key symptom in COPD [1,24,25]. As in earlier studies, we found moderate correlations between fatigue and dyspnea [5,15,17,18]. To our knowledge, this is the first study in which the relationship between fatigue and health status has been assessed in such detail. Fatigue was significantly related to almost all sub-domains of the main domains symptoms, functional impairment, and QoL. With respect to physiological functioning, fatigue was only related to the sub-domain exercise capacity but not to airflow, muscle strength, static lung volumes, or body composition. The significant (but low) correlation between fatigue and exercise capacity has not been reported earlier [16,19]. Fatigue was not significantly related to the sub-domain Airflow, which is consistent with

Table 5 Characteristics and distribution of fatigue (CIS-Subjective Fatigue score) for patients who participated at baseline and after 4 years (N=77)

	Baseline (n = 77)			After 4 years (n=77)			paired
	Mean	±SD	[95% CI]	Mean	±SD	[95% CI]	t-test
Gender (m/f),% (n)	83/17%	(64/13)					
Age	62.7	±8.6	[60.8-64.7]	66.8	±8.7	[64.9-68.8]	
Characteristics							
FEV_1% pred	52.9	±13.8	[49.8-56.0]	54.3	±16.9	[50.8-58.8]	n.s.
FEV_1 (Liter)	1.61	±0.48	[1.51-1.72]	1.59	±0.54	[1.40-1.65]	n.s.
FEV_1/FVC%	43.2	±12.4	[40.4-46.0]	42.5	±11.8	[39.7-45.2]	n.s.
TLC% predicted	103.4	±16.0	[99.8-107.1]	98.9	±14.4	[95.6-102.3]	n.s.
RV% predicted	127.4	±36.9	[119.0-135.7]	115.4	±30.3	[108.4-122.3]	n.s.
TLCO% predicted	70.1	±25.8	[64.3-76.0]	60.4	±23.9	[54.9-65.8]	p<0.01
BMI	25.7	±3.6	[24.9-26.5]	26.0	±4.0	[25.1-26.9]	n.s.
Fatigue							
Group	26.5	±11.2	[23.9-29.0]	31.2	±12.2	[28.4-33.9]	p<0.01
	%	(n)		%	(n)		
Normal fatigue	54.5%	(42)		36.4%	(28)		
Mild fatigue	24.7%	(19)		22.1%	(17)		
Severe fatigue	20.8%	(16)		41.6%	(32)		
Change in fatigue (MCID of 10 points)							
Fatigue improved				11.7%	(9)		
Fatigue same				54.5%	(42)		
Fatigue worsened				33.8%	(26)		

n.s.= non significant (p>0.01). *Abbreviations:* see Table 1; MCID, Minimally Clinically Important Difference

results found in other studies [15,16,19-21].

Some methodological comments have to be made. First, we only included patients with stable moderate to severe COPD without primary comorbidity. Although no significant correlations have been found between fatigue and airway obstruction in the present study and in other studies [15,16,19-21], results may be different for patients with mild or very severe COPD and for patients with primary comorbidity. Second, the sample size of the longitudinal data set was smaller than the baseline sample. However, no significant differences were found between participants and non-participants in the follow-up study on the characteristics measured at baseline. Nonetheless, we have to be cautious in generalizing these results due to the relatively small sample size.

CONCLUSIONS

Fatigue proved to be an important symptom in patients with moderate to severe COPD and appears to be related to many aspects of health status. Moreover, patients with abnormal fatigue have significantly more problems on many sub-domains of health status. In addition, our study also shows that after four years fatigue has relevantly increased in one third of patients. Hence, we will incorporate fatigue as a separate sub-domain in the NIAF.

Practice implications

We recommend that in the clinical management of patients with COPD assessment of fatigue is included as part of usual care, preferably by a standardized instrument (e.g. the Checklist Individual Strength) which corrects for normal fatigue. Future studies should be aimed at finding the causes of fatigue in COPD, since in most patients fatigue is getting worse over the years. This information is of importance for developing interventions aimed at improving fatigue.

Conflict of interest

None of the authors have any competing interests to declare.

Acknowledgments:

We are indebted to F. van den Elshout, MD (pulmonologist, Rijnstate Hospital, Arnhem) and R. Bunnik, MD (pulmonologist, Maas Hospital, Boxmeer) for their contribution to the recruitment of patients. We also are indebted to all participants for their time and effort to contribute to the study.

The study was supported by grants of the Dutch Asthma Foundation, GlaxoSmithKline, the Department of Medical Psychology, the Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, the Netherlands, the Organization for Health Research and Development (ZonMw), and PICASSO for COPD.

REFERENCES

1. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. European Respiratory Journal. 2004: 23:932-946.
2. Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. Journal of Pain and Symptom Management. 2009: 38:115-123.
3. Walke LM, Byers AL, Tinetti ME, Dubin JA, McCorkle R, Fried TR. Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure. Archives of Internal Medicine. 2007: 167:2503-2508.
4. Guyatt GH, Townsend M, Berman LB, Pugsley SO. Quality of life in patients with chronic airflow limitation. British Journal of Diseases of the Chest. 1987: 81:45-54.
5. Gift AG, Shepard CE. Fatigue and other symptoms in patients with chronic obstructive pulmonary disease: do women and men differ? Journal of Obstetric Gynecologic and Neonatal Nursing. 1999: 28:201-208.
6. Kinsman RA, Fernandez E, Schocket M, Dirks JF, Covino NA. Multidimensional analysis of the symptoms of chronic bronchitis and emphysema. Journal of Behavioural Medicine. 1983: 6:339-357.
7. Small SP, Lamb M. Measurement of fatigue in chronic obstructive pulmonary disease and in asthma. International Journal of Nursing Studies. 2000:, 37:127-133.
8. Ream E, Richardson A. Fatigue in patients with cancer and chronic obstructive airways disease: a phenomenological enquiry. International Journal of Nursing Studies. 1997: 34:44-53.
9. Small S, Lamb M. Fatigue in chronic illness: the experience of individuals with chronic obstructive pulmonary disease and with asthma. Journal of Advanced Nursing. 1999: 30:469-478.
10. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shields K, Turner-Lwaler PJ, Payne N, Newcombe RG, Lonescu AA, Thomas J, Turnbridge J. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. The Lancet. 2000: 355:362-368.
11. Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, Sanchis J. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest. 2000: 117:976-983.
12. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Systematic Review. 2006: CD003793.
13. Norweg AM, Whiteson J, Malgady R, Mola A, Rey M. The effectiveness of different combinations of pulmonary rehabilitation program components: a randomized controlled trial. Chest. 2005: 128:663-672.
14. Breslin E, van der Schans C, Breukink S, Meek P, Mercer K, Volz W, Louie S. Perception of fatigue and quality of life in patients with COPD. Chest 1998, 114:958-964.
15. Baghai-Ravary R, Quint JK, Goldring JJ, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease. Respiratory Medicine. 2009: 103:216-223.
16. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Comparison of discriminative properties among disease-specific questionnaires for measuring health-related quality of life in patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 1998: 157:785-790.

17. Reishtein JL. Relationship between symptoms and functional performance in COPD. Research in Nursing and Health. 2005: 28:39-47.
18. Woo K. A pilot study to examine the relationships of dyspnoea, physical activity and fatigue in patients with chronic obstructive pulmonary disease. Journal of Clinical Nursing. 2000: 9:526-533.
19. Wijkstra PJ, TenVergert EM, van der Mark TW, Postma DS, van Altena R, Kraan J, Koeter GH. Relation of lung function, maximal inspiratory pressure, dyspnoea, and quality of life with exercise capacity in patients with chronic obstructive pulmonary disease. Thorax. 1994: 49:468-472.
20. Berry MJ, Adair NE, Rejeski WJ. Use of peak oxygen consumption in predicting physical function and quality of life in COPD patients. Chest. 2006: 129:1516-1522.
21. Oga T, Nishimura K, Tsukino M, Hajiro T, Sato S, Ikeda A, Hamadas C, Mishima M. Longitudinal changes in health status using the chronic respiratory disease questionnaire and pulmonary function in patients with stable chronic obstructive pulmonary disease. Quality of Life Research. 2004: 13:1109-1116.
22. Vercoulen JH, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavioural Medicine. 2008: 15:263-279.
23. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
24. Beurskens AJHM, Bultmann U, Kant IJ, Vercoulen JHMM, Bleijenberg G, Swaen GMH. Fatigue amongst working people: validity of a questionnaire measure. Occupational and Environmental Medicine. 2000: 57:353-357.
25. Bultmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant I. Measurement of prolonged fatigue in the working population: determination of a cutoff point for the checklist individual strength. Journal of Occupational Health Psychology. 2000: 5:411-416.
26. Repping-Wuts H, Fransen J, van Achterberg T, Bleijenberg G, van Riel P. Persistent severe fatigue in patients with rheumatoid arthritis. Journal of Clinical Nursing. 2007: 16:377-383.
27. Servaes P, Gielissen MF, Verhagen S, Bleijenberg G. The course of severe fatigue in disease-free breast cancer patients: a longitudinal study. Psychooncology. 2007: 16:787-795.
28. Tammeling GJ, Quanjer PH. Standardized lung function testing. European Respiratory Journal. 1993: 6:5-33.
29. Maillé AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA. The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QoL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91:297-309.
30. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical Care. 1981: 19:787-805.
31. Tryon WW. Activity measurement in psychology and medicine. New York: Plenum Press; 1991.
32. Vercoulen JHMM, Bazelmans E, Swanink CMA, Fennis JFM, Galama JMD, Jongen PJH, Hommes OR, van der Meer JWM, Bleijenberg G. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. Journal of Psychiatric Research. 1997: 31:661-673.
33. Arrindell WA, Ettema JHM. SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets & Zeitlinger; 1986.

34. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behavaviour Research and Therapy. 1997: 35:785-791.
35. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. Journal of Personality Assessment. 1985: 49:71-75.

CHAPTER 3

Development of a battery of instruments for a detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument

Jeannette B Peters
Leonie Daudey
Yvonne F Heijdra
Johan Molema
P N Richard Dekhuijzen
Jan H Vercoulen

Quality of Life Research. 2009: 18(7):901-912

ABSTRACT

Objective

To compose a battery of instruments that provides a detailed assessment of health status in COPD, but that is applicable and clinically meaningful in routine care.

Methods

In a previous study, we developed the Nijmegen Integral Assessment Framework (NIAF) that organizes existing tests and instruments by the sub-domains of health status they measure. Based on clinical and statistical criteria (correlation coefficients and Cronbach alpha's) we selected for each sub-domain instruments from the NIAF. A COPD-study group was used to determine c-scores, and two control groups were used to determine the score ranges indicating normal functioning versus clinically relevant problems for each sub-domain. Existing questionnaire completion software (TestOrganiser) was adapted to enhance clinical applicability.

Results

The Nijmegen Clinical Screening Instrument measures eleven sub-domains of physiological functioning, symptoms, functional impairment, and quality of life. The TestOrganiser automatically processes the data and produces the graphical PatientProfileChart, which helps to easily interpret results. This envisages the problem areas and discrepancies between the different sub-domains.

Conclusions

The NCSI provides a valid and detailed picture of a patient's health status within 15-25 min. In combination with the PatientProfileChart, the NCSI can be used perfectly in routine care as screening instrument and as a guide in patient-tailored treatment.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, progressive, and incapacitating disease. Traditionally, treatment of COPD is focused on improving or maintaining physiological functioning of the patient. However, in the past decade, it is recognized that besides physiological functioning also symptoms, functional limitations and quality of life (QoL) are important domains of health status in these patients [1-2].

Studies have shown that symptoms, functional impairment, and QoL are relatively unrelated to physiological functioning [3-5]. In a previous study we also have shown that these four main domains of health status were shown to be subdivided into 15 relatively unrelated sub-domains [6]. An individual patient may experience clinically relevant problems in some of these sub-domains, but not in other sub-domains. As a consequence, to tailor treatment to the specific needs of the individual patient it is necessary to obtain an integral and detailed picture of health status of all sub-domains.

In routine care, physiological functioning is measured by lung function tests. Although, many generic and disease specific questionnaires are available to measure symptoms, functional impairment and QoL [3,7], these three main domains commonly are not measured in routine care. A major reason for this is that current questionnaires are not suitable for application in routine care. This has several causes. First, questionnaires commonly consist of many items and are therefore time-consuming. Second, the scoring of questionnaires is often complex and has to be done by hand which is also time-consuming. Third, the clinical meaning of a particular score is often unclear due to the lack of adequate normative data. Normality cannot be defined by absence of for example symptoms. As patients with COPD are often elderly, the presence of an elevated score can also be the result of normal ageing instead of being the result of having COPD. Moreover, symptoms such as fatigue or shortness of breath may be experienced by healthy persons as well. Hence, it is important to know whether a score represents normal functioning or clinically relevant problems. Fourth, in a previous study, we found that existing questionnaires measure only one to three aspects of health status [6]. In addition, we have shown that there is considerable overlap between questionnaires with respect to the specific sub-domains they measure. This implicates that, for an integral and detailed assessment of health status, a combination of several instruments is required in which overlap should be avoided.

Consequently, the following criteria must be fulfilled to permit adequate assessment of health status suitable and useful in routine care: 1) a broad spectrum of aspects of health status has to be measured to obtain a comprehensive and detailed picture; 2) instruments should be as short as possible, but still have enough items to warrant adequate reliability; 3) overlap should be avoided; 4) scoring must be simple and results should be available immediately, preferably this should be automated; and 5) results should be easy to interpret and should indicate if a particular score indicates normal functioning or clinically relevant problems. Such an instrument would provide the clinician with a tool to identify patients

who need additional treatment and provides a detailed picture on the type and severity of problems in health status of an individual patient, and thereby can help the clinician in patient-tailored treatment. In addition, it also could be used for outcome assessment, as part of an intervention, and for research studies.

The aim of the present study was to compose a battery of existing questionnaires that fulfills all above-mentioned criteria for clinical applicability in a routine care outpatient setting. In this process we used the Nijmegen Integral Assessment Framework (NIAF) [6] as a guide for the selection of instruments. The NIAF is an evidence-based framework that organizes tests and questionnaires by indicating which sub-domains of health status actually are measured by specific (sub-)scales of various existing instruments. Data of matched control groups were used to determine cut-offs for each instrument to indicate normal functioning versus clinically relevant problems. In addition, existing software for computerized questionnaire completion was adapted specifically to facilitate clinical applicability of the test battery and easy interpretation of results.

METHOD

Subjects

COPD- study group

For the selection of instruments of the Nijmegen Clinical Screening Instrument (NCSI) we used the data from a sample of COPD patients that are representative for patients with stable COPD (GOLD II and III), with no primary co-morbidity, in routine care at outpatient clinics. This COPD-study group was recruited from three different pulmonary outpatient clinics in the Netherlands: University Lungcenter Dekkerswald of the Radboud University Nijmegen Medical Centre, Maas Hospital Boxmeer and Rijnstate Hospital Arnhem. Inclusion criteria were: diagnosis of GOLD II/III (FEV_1% predicted between 30% and 80%), FEV_1/FVC <70%, and reversibility of obstruction <12%. Exclusion criteria were: primary co-morbidity that may dominate health status, recent participation in a rehabilitation program (within previous six months), inability to speak or read Dutch, acute exacerbation of COPD, and inability to completely adhere to the research protocol. Screening the patient charts resulted into 361 eligible patients. A pulmonologist asked these patients for permission to be called by the investigator, and 316 (88%) agreed to be called for further information. One hundred-sixty-eight patients (47%) participated in this study (see Table 1 for patient characteristics). Reasons for non-participation were diverse; predominantly being too busy, refusing cycle-ergometry and travel problems. Patients gave informed consent and the local Ethics Committee approved this study.

Control samples

To determine the score range of the selected instruments that represents clinically relevant problems, we recruited patients with COPD included in a clinical multi-disciplinary

Table 1 Patient characteristics expressed in number (%) unless stated otherwise of the COPD outpatient study group (OP), patients included in pulmonary rehabilitation (PR), and healthy controls (HC)

	OP		PR		HC	
N	168		131		69	
Male	131	(78.0%)	89	(67.9%)	48	(69.6%)
Age (mean ±SD)	64.5	±9.1	62.1	±7.3	62.4	±7.8
range	43-80		46 -78		41-76	
FEV_1% pred (mean ±SD)	51.6	±13.6	35.0	±13.0	111.7	±14.8
GOLD						
Stage 1	0	(0%)	0	(0%)	0	(0%)
Stage 2	88	(52.4%)	18	(13.7%)	0	(0%)
Stage 3	80	(47.6%)	63	(48.1%)	0	(0%)
Stage 4	0	(0%)	50	(38.2%)	0	(0%)
BMI (mean (SD))	25.6	(4.1)	24.4	(4.2)	26.4	(3.9)
Education						
Low	85	(52.1%)	68	(51.9%)	20	(29.0%)
Middle	48	(29.4%)	38	(29.0%)	18	(26.1%)
High	30	(18.4%)	25	(19.1%)	21	(44.8%)
Personal Situation						
Partner	137	(84.0%)	105	(80.1%)	52	(75.4%)
Divorced	7	(4.3%)	6	(4.6%)	8	(11.6%)
Widowhood	11	(6.7%)	9	(6.9%)	3	(4.3%)
Single	8	(4.9%)	11	(8.4%)	6	(8.7%)

Pulmonary rehabilitation program at the University Lungcenter Dekkerswald of the Radboud University Nijmegen Medical Centre. A key requirement for inclusion in this program is that patients have to experience clinically relevant problems in multiple areas of health status. The decision on this requirement was based on a 3-days intake procedure, in which elaborate assessments, physiological tests, and clinical interviews by seven disciplines (pulmonologist, psychotherapist, physiotherapist, nurse, dietitian, psychomotor therapist, social worker) took place. The results of these assessments and interviews are evaluated in a multi-disciplinary discussion. Inclusion criteria were: diagnosis of COPD [8] and clinically relevant problems in multiple areas of health status. Exclusion criteria: mild or isolated problems in health status and inability to speak or read Dutch. Subjects were matched to the COPD-study group by age and sex. See Table 1 for a description of this sample.

To determine the score range of instruments indicating normal functioning, we recruited healthy controls by an advertisement in a regional newspaper. Exclusion criteria were: having asthma or COPD, being under regular treatment of any specialist and/or inability to speak or read Dutch. The subjects were screened for absence of chronic illnesses by one of the investigators (LD). Subsequently, lung function testing was performed. Based on all assessments a pulmonologist (JM) decided whether a person could be included or not. Subjects were matched on age and sex to the COPD-study group. See Table 1 for a description of this sample.

Measurements

In a previous study, we defined four domains of health status; Physiological Functioning, Symptoms, Functional Impairment, and QoL [6]. These four main domains of health status were found to be subdivided into 15 relatively unique sub-domains, which together constitute the NIAF for COPD. See Figure 1 for a general description of the development and validation of the NIAF. For a detailed description on the development and validation of the NIAF see elsewhere [6].

In a recent, yet, unpublished study, we found fatigue to be an important symptom in COPD that is relatively independent to the other sub-domains. For that reason, fatigue was included in the framework as a separate sub-domain of the main domain symptoms. Table 2 shows the instruments that measure the sub-domains of health status.

Questionnaire completion was performed by the TestOrganiser, which is a computerized questionnaire system developed by the Department of Medical Psychology and the Department of Instrumental Services of the Radboud University Nijmegen Medical Centre [6]. Questionnaires are presented in the same layout as paper-and-pencil versions, items cannot be skipped, and both scoring and data storage are automated.

Construction of the Nijmegen Clinical Screening Instrument

The NIAF organizes existing instruments by the sub-domains of health status they measure. Each sub-domain was measured by several tests or instruments or subscales of instruments (Table 2), and can be used interchangeably. Based on the following criteria we selected for each sub-domain one or two instruments for inclusion of the NCSI.

A. Preliminary selection of instruments

1. The scores on selected instruments should show a correlation of >0.70 with the original NIAF-STS [9].
2. The selected instruments must be completed in as little time as possible (preferably <30 minutes), in other words a minimum number of items, but should show good reliability (Cronbach's alpha >0.70).
3. Although all instruments included in the NIAF are clinically relevant, in the selection process of instruments we also considered which instrument was most clinically relevant. These decisions were based on clinical experience of the pulmonologists (JM, YH, RD) and the clinical psychologist (JV).

B. Statistical analysis on the preliminary selection

1. For each sub-domain of health status, selected instruments were combined into a sub-domain total score (NCSI-STS) by adding scores of respective instruments. Spearman correlation coefficients between the original NIAF-STS and the new NCSI-STS were calculated and had to be higher than 0.70, which is considered a criterion for instruments to measure the same concept [9,10].

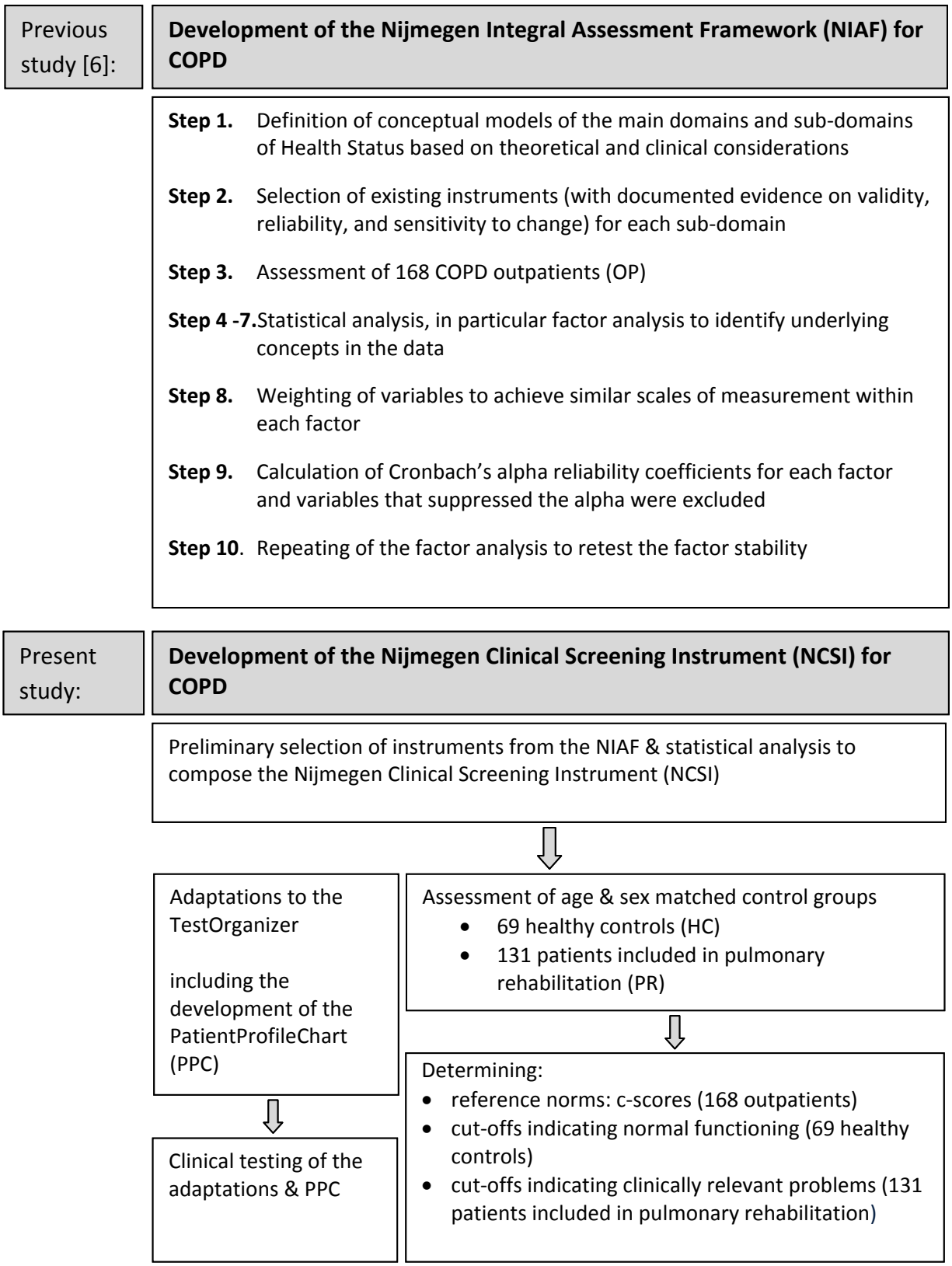


Figure 1 Main stages of the development of the Nijmegen Integral Assessment Framework (NIAF) for COPD (previous study) and the development of the Nijmegen Clinical Screening Instrument (NCSI) for COPD (present study)

Table 2 Sub-domains of the Nijmegen Integral Assessment Framework (NIAF), their corresponding instruments, subscales/measurements. The preliminary selection of instruments for the Nijmegen Clinical Screening Instrument are indicated in **bold** type face

	Sub-domain	Instrument	Subscale/ Measurement	correlation with NIAF-STS	Number of items
Physiological Functioning	Exercise Capacity	V_{max} 29, Sensor Medics	VO_2 maximum% predicted	.79	
			Heart rate maximum% predicted	.74	
			TLCO % predicted	.73	
			BE delta	.71	
	Static Lung Volumes	Masterscreen PFT spirometer/	**TLC % predicted**	**.95**	
		diffusion, Jaeger	**RV % predicted**	**.95**	
	Airflow	Masterscreen PFT spirometer/	**Post-bronchodilator FEV_1% predicted**	**-.91**	
		diffusion, Jaeger	MEF50 % predicted	-.81	
			VE % predicted	.72	
	Gas Exchange	V_{max} 29, Sensor Medics	Delta (A-a)DO2 (kPa)	*	
			Delta PaCO2 (kPa)	*	
	Muscle Strength	Validyne CD23	PE_{max}% predicted	-.80	
			PI_{max} % predicted	-.75	
			Quadriceps % predicted	-.72	
	Body Composition	W/H^2	**BMI**	**-.95**	
		Bodystat	FFMI	-.95	
Symptoms	Subjective Symptoms	PARS-D [6]	**Global Dyspnea Activity**	**.89**	**1**
			Dyspnea Activity	.89	14
			Global Dyspnea Burden	**.85**	**1**
		QoL-RIQ [20]	Breathing Problems	.76	9
	Dyspnea Emotions	DEQ [6]	DEQ-Mood	.89	3
			DEQ-Frustration	**.84**	**3**
			DEQ-Anxiety	**.79**	**3**
	Expected Dyspnea	PARS-D [6]	Expected Dyspnea	1.00	14
	Fatigue	CIS [21]	**Fatigue**	**1.00**	**8**
	Actual Activity	Aktometer [22]	Aktometer Mean	1.00	12 days
Functional Impairment	Behavioral Impairment	SIP [23,24]	**SIP Home Management**	**.82**	**10**
			SIP Ambulation	**.81**	**12**
			SIP Body Care & Movement	.77	22
			SIP Mobility	.69	10
	Subjective Impairment	QoL-RIQ [20]	**QoL-RIQ General Activities**	**.90**	**4**
			QoL-RIQ Social Activities	.83	7
		Global Impairment [6]	Global impairment	.78	1
		SIP [23,24]	SIP Social Interaction	.75	20
			SIP Burden	.71	5
Quality of Life	General QoL	BDI [25]	**BDI Primary Care**	**.83**	**7**
		SWLS [26]	**SWLS-Total**	**.81**	**5**
		SCL [27]	SCL Anxiety	.80	10
	HRQol	Satisfaction-Physical [6]	**Satisfaction Physical**	**.88**	**1**
		Satisfaction-Future [6]	**Satisfaction Future**	**.88**	**1**
	Satisfaction Relations	Satisfaction-Spouse [6]	**Satisfaction Spouse**	**.84**	**1**
		Satisfaction-Social [6]	**Satisfaction Social**	**.84**	**1**

Abbreviations: %, percentage of predicted ; BDI, Beck Depression Inventory**;** BE, Base Excess; BMI, Body Mass Index; CIS, Checklist Individual Strenght; DEQ, Dyspnea Emotions Questionnaire; FEV_1, Forced Expiratory Volume in one second postbronchodilator value; FFMI, Fat Free Mass Index; MEF50, mid-expiratory Flow at 50% of forced vital capacity; PARS-D, Physical Activity Rating Scale –Dyspnea; PImax, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; QoL, Quality of Life; HrQoL, health related quality of life; QoL-RIQ, Quality of Life for Respiratory Illness Questionnaire; RV, Residual Volume; TLC, Total Lung Capacity; TLCO, transfer capacity (of lung) for carbon monoxide; SCL, Symptom Checklist; SIP, Sickness Impact Profile; SWLS, Satisfaction With Life Scale; VE, minute ventilation ;VO_2max, maximal oxygen uptake. *= non-linear variables

2. To test possible overlap between the sub-domains the inter-correlations between all NCSI-STS were calculated by spearman coefficients, and should be lower than 0.70.
3. The Cronbach's alpha reliability coefficients (internal consistency) of each NCSI-STS should be at least be moderate (>0.50) and preferably >0.70 [9].

Construction of normative data

For each subscale, the total score range of the COPD study group was transformed to c-scores. C-scores are similar to percentile scores, but differentiate more in the extremes of the score range and correct for skewed distributions. The score-range is 1-11, and the scores refer to the following percentiles respectively : 1.2-4.0-10.6-22.7-40.1-59.9-77.3-89.4-96.0-98.8-100%. For each instrument the score belonging to the 80th percentile of the healthy controls was used as the maximal score of normal functioning (green colored score range), and the score belonging to the 20th percentile of the pulmonary rehabilitation patients was used as the minimum score representing clinically relevant problems (red colored score range). The area between green and red has been labeled 'elevated'(yellow).

New features of the TestOrganiser

The TestOrganiser was originally developed for the purpose of data collection in research. In the past three years, the TestOrganiser has been implemented in our inpatient and outpatient clinic to develop and test clinical applicability and patient acceptability in routine care. The software of the TestOrganiser was revised in several aspects and new features were developed. These revisions particularly concerned automated data processing. The most important new feature is the graphical presentation of results on the level of an individual patient (the PatientProfileChart) to facilitate ease of interpretation of results for clinical purposes.

RESULTS

No significant differences were found between the COPD-study group and the two control groups with respect to age and sex (Table 1).

Construction of the Nijmegen Clinical Screening Instrument

A. Preliminary selection of instruments

The preliminary selection of instruments for the NCSI is shown in Table 2. The instruments in bold were selected for the NCSI. The sub-domains exercise capacity, gas exchange and muscle strength require cycle-ergometry testing and muscle strength tests are too time-consuming for use in a routine care outpatient setting and, therefore, were excluded. The sub-domains expected dyspnea (main domain symptoms) and actual physical activity (main domain functional impairment) were excluded because these tests also are too time-

consuming: the PARS-Expected Dyspnea consist of 20 items and the accelerometer has to be worn for 12 days.

With respect to the sub-domain dyspnea emotions (main domain symptoms) we included dyspnea related anxiety instead of dyspnea-related mood despite the higher correlation of the latter, because dyspnea-related anxiety is far more common in COPD than dyspnea-related depressed mood. With respect to the sub-domain subjective symptoms (main domain symptoms) we included the PARS-D Global Dyspnea Burden (1 item) instead of the PARS-D Dyspnea activity (14 items) for reasons of brevity.

B. Statistical analysis on the preliminary selection

The correlations between the sub-domain total scores of the NIAF (NIAF-STS) and the NCSI (NCSI-STS) all exceeded 0.70, which indicates that the NCSI-STS are conceptually similar to the NIAF-STS (Table 3). In addition, all Cronbach's Alpha's of the NCSI-STS were >0.70, except those of general QoL (0.61) and satisfaction relations (0.64) (Table 3).

Tabel 3 Correlations between the sub-domains measured by the NCSI-sub-domain total scores (NCSI-STS) versus the NIAF-sub-domain total scores (NIAF-STS) ($p<0.01$) and Cronbach's alpha reliability coefficients of all NCSI-STS

Domain	Sub-domain	Subscale/Measurement	Correlation NCSI-STS vs. NIAF-STS	Number of items	Cronbach's alpha
Physiological Functioning	Static Lung Volumes	TLC% predicted	.99		--
		RV% predicted			
	Airflow	Post-bronchodilator FEV_1 % pred.	-.91		--
	Body Composition	BMI	-.95		--
Symptoms	Subjective Symptoms	PARS-D Global Dyspnea Activity	.93	2	.85
		PARS-D Global Dyspnea Burden			
	Dyspnea Emotions	DEQ Frustration	.96	6	.82
		DEQ Anxiety			
	Fatigue	CIS fatigue	1.00	8	.83
Functional Impairment	Behavioral Impairment	SIP Home Management	.91	22	.72
		SIP Ambulation			
	Subjective Impairment	QoL-RiQ General Activities	.90	4	.88
Quality of Life	General QoL	Satisfaction With Life Scale	.94	12	.61
		BDI Primary Care			
	HRQoL	Satisfaction Physical	1.00	2	.71
		Satisfaction Future			
	Satisfaction Relations	Satisfaction Spouse	1.00	2	.64
		Satisfaction Social Relations			

Abbreviations: see table 2

In general, there was none or at best moderate overlap between the sub-domains of the NCSI-STS as expressed by non-significant to at best moderate inter-correlations (Table 4).

Additional items were added to measure smoking-status (yes/no) and willingness to quit smoking (yes/no).

Construction of normative data

Characteristics of the sub-domains included in the NCSI for all study groups are presented in Table 5. As expected, in healthy controls there was a strong floor effect on disease-related domains: symptoms (except fatigue) and functional impairment. In general, there were no evident problems related to floor and ceiling effects in both COPD groups. As expected, the pulmonary rehabilitation control group showed the highest scores on all sub-domains and healthy controls the lowest.

Table 4 Intercorrelations between the Nijmegen Clinical Screening Instrument sub-domain total scores (NCSI-STS)

Main domain		Physiological Functioning			Symptoms			Functional Impairment		Quality of Life		
	Sub-domain	Static Lung Volumes	Obstruction	Body Composition	Subjective Symptoms	Dyspnea Emotions	Fatigue	Behavioral Impairment	Subjective Impairment	General QOL	HRQoL	Satisfaction Relations
Physiological Functioning	Static Lung Volumes	1.00										
	Obstruction	-	1.00									
	Body Composition	-	0.28	1.00								
Symptoms	Subjective Symptoms	-	-0.28	-	1.00							
	Dyspnea Emotions	-	-	-	0.27	1.00						
	Fatigue	-	-	-	0.52	0.30	1.00					
Functional Impairment	Behavioral Impairment	-	-	-	0.48	0.25	0.43	1.00				
	Subjective Impairment	-	-	-	0.65	0.42	0.60	0.54	1.00			
Quality Of life	General QOL	-	-	-	0.45	0.41	0.44	0.44	0.59	1.00		
	HRQoL	-	-	-	0.46	0.40	0.55	0.49	0.62	0.63	1.00	
	Satisfaction Relations	-	-	-	0.29	0.35	0.39	0.30	0.48	0.49	0.54	1.00

Only correlations with p<0.01 are printed

Table 5 Characteristics of the three groups on the sub-domains of health status; the minimal, maximal score for each sub-domain, mean ±SD, % patients with the lowest possible score (floor) and % of patients with the highest possible score (ceiling)

		COPD outpatient study group			patients included in pulmonary rehabilitation			healthy controls		
Domain/sub-domain	Min - max	Mean ±SD	floor	ceiling	Mean ±SD	floor	ceiling	Mean ±SD	floor	ceiling
Symptoms										
Subjective Symptoms	2-20	7.49 ±4.34	19.0 %	0 %	12.81 ±4.06	0 %	3.8 %	2.30 ±1.33	91.0 %	0 %
Dyspnea Emotions	6-24	9.78 ±3.19	14.3 %	0.6 %	12.28 ±3.86	2.5 %	0.8 %	6.29 ±1.07	85.5 %	0 %
Fatigue	8-56	27.29 ±11.40	3.6 %	3.0 %	39.08 ±10.33	0 %	4.6%	16.43 ±7.70	21.7 %	0 %
Functional Impairment										
Subjective Impairment	0-135.5	15.20 ±12.82	18.5 %	0 %	29.02 ±14.83	0 %	0 %	1.74 ±3.69	76.8 %	0 %
Behavioral Impairment	4-28	9.78 ±4.78	14.3 %	0.6 %	16.08 ±5.63	0.8 %	3.1 %	4.20 ±0.90	92.8 %	0 %
Quality of Life										
General QoL	1-101.6	14.18 ±12.07	7.1 %	0 %	23.42 ±12.80	0.8 %	0 %	8.27 ±7.52	5.8 %	0 %
HrQoL	2-10	4.07 ±1.68	16.7 %	0.6 %	6.08 ±1.57	0 %	0 %	2.64 ±0.94	58.0 %	4.3 %
Satisfaction Relations	2-10	3.11 ±1.36	44.6 %	0 %	3.86 ±1.67	25.2 %	1.5 %	3.13 ±1.92	56.5 %	4.3 %

FEV_1%: Forced expiratory volume in 1 second; BMI: body mass index; p-values in bold: significant differences between the phenotypes

New features of the TestOrganiser

To enable patients with no prior computer experience to complete the questionnaires easily, a simple response-board was developed with a minimum of (large) buttons. A network function was integrated that enables immediate access to the results after test completion on every computer in the hospital. The most important new feature is the automatic production of graphical representations of the results: the PatientProfileChart (see Figure 2).

The PatientProfileChart (PPC) provides a graphical presentation of the scores of an individual patient. Each column represents a specific instrument within a sub-domain. All score ranges are based on the reference sample (COPD-study group) and are expressed as c-scores. The *x* represents the score of the individual patient. First, the *x* indicates how a patient scores in relation to the general COPD population. For example, the patient in Figure 2 had a raw score on Depression of 3 which falls in the 7^{th} C-score of the COPD reference sample. This means that 77,3% of the reference sample had a lower score. Second, the score range of each instrument is divided into coloured ranges, which allow absolute interpretations. The green score range indicates 'normal functioning', the yellow score range indicates 'mild problems', and the red score range indicates 'clinically relevant problems'. The patient in Figure 2 scored in the yellow area ('mild problems'). Thus, although this patient had a higher score than 77% of the COPD reference sample (7^{th} C-score), still this score did not indicate clinically relevant problems.

DISCUSSION

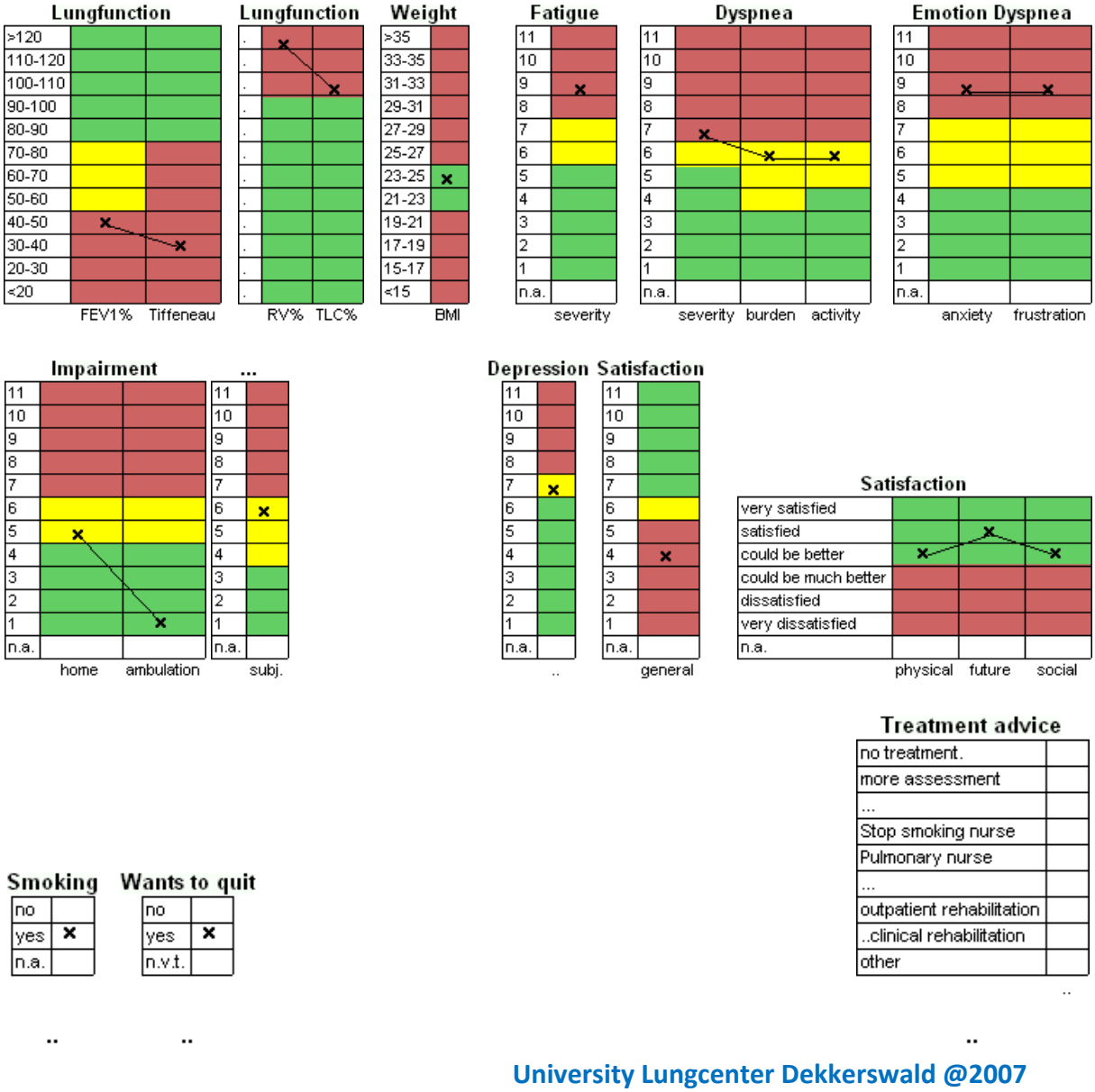
In the present study, we developed the Nijmegen Clinical Screening Instrument (NCSI), that is short enough to be completed in routine care, but stills provides much detail on a patient's health status. In addition, the TestOrganiser was adapted to further improve clinical applicability of the NCSI in routine care. To facilitate interpretation of a patient's scores, we developed the PatientProfileChart that presents results graphically. In addition, we determined cut-offs based on reference groups indicating whether a particular score indicates normal functioning or clinically relevant problems.

Guidelines for treatment of COPD emphasize the importance of maintaining and optimizing health status [8;11-12], and describe for every COPD severity stage (based on the degree of airway obstruction; I-IV) what type of treatment is indicated. Pulmonary rehabilitation, for example, is indicated for GOLD stages III-IV. However, health status consists of four main domains: physiological functioning, symptoms, functional impairment, and quality of life [1,2,6,13], divided into at least 15 unique sub-domains [6]. Given the findings of many studies showing that FEV_1 is poorly related to symptoms, functional impairment, and quality of life [3-5;14] it is impossible to determine the status of other sub-domains of health status on the basis of FEV_1 alone. Thus, FEV_1 gives no information on any aspect of health status other than airway obstruction, and as such is a poor indicator for

Nijmegen Clinical Screening Instrument (NCSI)

Patient characteristics 28-03-2008

Name
Date of birth
Sex
PatiëntNumber
ResearchNummer
Notes



University Lungcenter Dekkerswald @2007

Figure 2 The PatientProfileChart; a graphical representations of the patients' results

specific interventions such as pulmonary rehabilitation. Consequently, tailoring treatment to the needs of the individual patient requires an integral and detailed picture of the individual patient's health status by measuring of all four main domains and their many sub-domains.

Many generic and disease-specific instruments have been developed to measure health status in COPD patients [3,7]. However, most of these instruments are rather lengthy, scoring is time-consuming, commonly measure only few aspects of health status, and in many cases it is unclear whether a score represents normal functioning or clinically relevant problems, due to the lack of normative data. In addition, as existing instruments measure only few aspects of health status, the need for a detailed assessment of health status to enable patient-tailored treatment requires the combination of multiple instruments. However, such a battery of instruments would diminish clinical applicability even further as this would increase problems with regard to the length of instruments, time-consuming scoring procedures, as well as the overlap found between instruments [6].

The need for short questionnaires that allow measurement of symptoms, functional impairment, and quality of life in routine care has been acknowledged by other researchers. Several instruments have been developed for this purpose; the Clinical COPD Questionnaire (CCQ) [15], the Respiratory Illness Questionnaire–monitoring 10 (RIQ-MON10) [16], and the EuroQoL (EQ-5D) [17]. These instruments are short (six to ten items), and have shown good validity and reliability. However, the CCQ measures only three sub-domains of health status, the RIQ-MON10 measures only two sub-domains, and the EQ-5D measures only three sub-domains. Although, these instruments are short and easy to score, these do not provide a detailed picture of the patient's health status, and lack normative data indicating normal functioning versus clinically relevant problems. Hence, these instruments still do not satisfy all requirements for clinical applicability as pointed out in the introduction.

We did not develop a new instrument, as we did not want to add to the abundance of instruments already available, but we set out for a new approach which would render existing instruments suitable for use in routine care. We composed a battery of existing instruments with a minimum number of items, but with a maximum of detail of health status, a minimum of overlap between instruments, and good reliability and validity. Although clinical considerations did play a role in the selection process of instruments, decisions were not based on personal preferences of the researchers, or on how frequent a particular instrument is used in COPD research. The selection of instruments from the empirically validated integral assessment framework of health status in COPD [6], the NIAF, was primarily guided by statistical analyses. The NIAF contains 16 sub-domains of health status covering the main domains physiological functioning, symptoms, functional impairment, and quality of life. In addition, this framework provides additional validity information on many existing instruments: it indicates what sub-domain(s) of health status specific instruments measure and it indicates which instruments measure the same sub-domains of health status.

Although the NCSI enables a quick (15-25 minutes) and detailed assessment of health status, typical questionnaire problems such as complex scoring procedures and the problem

of interpretability of results remained. To provide a solution for these problems the software of the TestOrganiser was adapted. This involved automatic scoring, a network facility, and the development of a special response-board. After instructions, additional questions of patients predominantly were related to the content of the questionnaire items, and rarely with regard to computer operating.

The most important new feature of the TestOrganiser is the PatientProfileChart. Immediately after completion of the NCSI, the PatientProfileChart is generated by the TestOrganiser, is available on every authorized computer in the clinic, and can immediately be discussed with the patient. The interpretation of the PatientProfileChart is very easy: for the clinician, but also for the patient. A short training is sufficient to learn clinicians how to interpret the PatientProfileChart. The colored areas of the score range of each instrument indicate whether a patient shows normal functioning in a particular sub-domain of health status or clinically relevant problems.

Psychometric properties of the NCSI are good. The correlations between the NCSI-STS and the corresponding NIAF-STS were high and well above the criterion for conceptual similarity. Within the NCSI there was little overlap between the NCSI-STS as expressed by non-significant to at best moderate inter-correlations. This also indicates that each sub-domain of the NCSI represents a unique aspect of a patient's health status. The internal consistency of the NCSI-sub-domain total scores in general were good, except the general Qol and satisfaction relations.

Some methodological issues need to be addressed. First, in the present study the test-retest reliability and the responsiveness-to-change of the instruments used to measure the sub-domains of health status were not tested. However, inclusion of instruments with adequate psychometric properties was one of the selection criteria for the NIAF. For most of the included instruments test-retest reliability and responsiveness-to-change were found adequate in other studies [18,19,21,24]. Second, not all sub-domains of health status are measured by the NCSI. Some sub-domains required measurements that are too time-consuming for use in routine care at an outpatient clinic (e.g. cycle-ergometry testing, accelerometry). Future studies are needed to find alternatives that can be used for measuring those sub-domains in routine care. Nevertheless, the decision on what specific measurements are too time-consuming also may depend on specific settings. The final issue refers to the use of control groups and the need for cut-offs. Normal functioning cannot be defined by absence of symptoms or functional impairment, for example, due to effects of normal ageing. This means that the upper part of the score range in healthy subjects indicates abnormal functioning. Therefore, we used the 80th percentile of healthy controls as the upper limit of normal functioning. Similarly, 'clinically relevant problems' cannot be defined by the mere presence of such problems. For example, healthy subjects may experience fatigue or shortness of breath as well. In addition, even patients with multiple and severe problems in health status (the inpatient pulmonary rehabilitation controls) may not have problems in all sub-domains. So, we assumed that for each sub-domain the lower part of the score range of the rehabilitation patients overlaps with the score range of normal

functioning or mild problems. Therefore, we chose the 20th percentile of the pulmonary rehabilitation patients as the cut-offs for clinically relevant problems. Although the method we used to calculate cut-off scores indicating normal functioning versus clinically relevant problems is an accepted approach [25], to a certain degree these cut-offs remain arbitrary. However, decisions on, for example, which patients do need additional treatment versus those who do not, never depend on one single sub-domain, but on the profile on all sub-domains. Most important criteria in this respect are the number of sub-domains showing clinically relevant problems and discrepancies between the severity of physiological sub-domains versus the sub-domains measuring symptoms, functional impairment, or quality of life. This may render the arbitrariness of cut-offs less problematic. In addition, the clinical relevance of the cut-offs (i.e. the profiles) were clinically tested during 3 years in different settings, and proved to be quite accurate.

The NCSI can be used for several clinical purposes. *Screening and monitoring*. In our centre, every year the patient completes the NCSI during a regular visit. In this way, problems in all four domains of health status are revealed in an early stage.

Decision making. The profile of the PatientProfileChart indicates which type of intervention would be required for this individual patient (e.g. pulmonary nurse, an outpatient or multi-disciplinary pulmonary rehabilitation program). As pointed out above such decisions are based on the profile of all sub-domains. Additionally, the discussion of the PatientProfileChart with patient and partner elucidates the mechanisms underlying the problems in health status. This provides additional information on which type of intervention is best suited.

Motivational intervention. The NCSI and PatientProfileChart can be used as an intervention to increase the patient's motivation to adopt adequate health behaviors (e.g. stop smoking, regular exercise) or to enroll in additional treatment (e.g. rehabilitation program). This is simply done by discussing the PatientProfileChart with the patient and his partner. The motivational effect is achieved by several psychological mechanisms 'hidden' in this procedure. The most important are firstly, results are presented graphically, which has much greater impact than words, and thereby powerfully increases awareness of the severity of his problems. Secondly, the profile is the resultant of responses of the patient himself and does not reflect the opinion of the clinician. This increases commitment and avoids conflicting opinions. The NCSI can also be used for *outcome assessment and research purposes*.

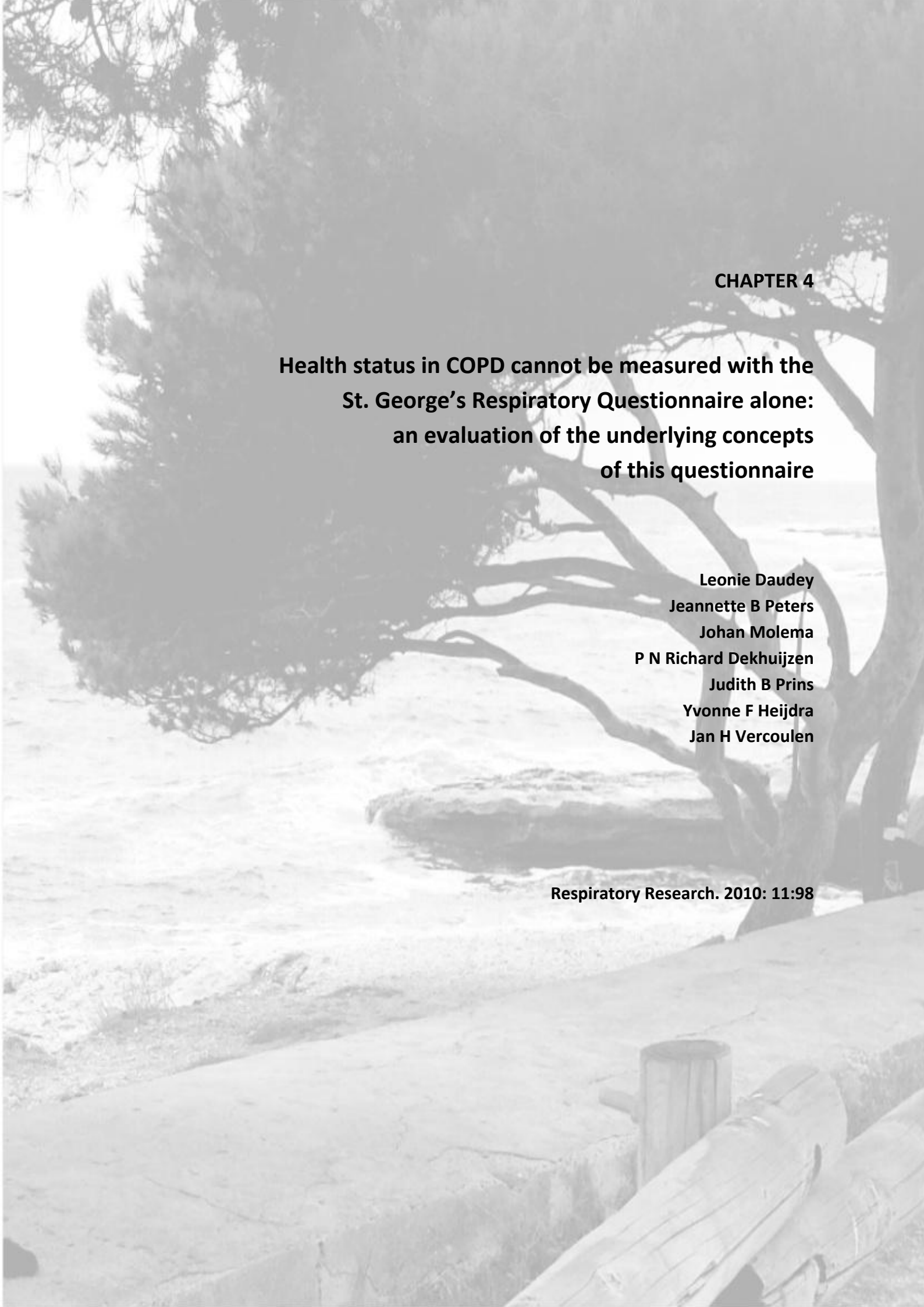
In conclusion, in this study we composed a battery of instruments that enables the clinician to obtain a valid, reliable, and detailed picture of a patient's health status by measuring multiple sub-domains covering all four main domains. In combination with the TestOrganiser and the PatientProfileChart, the NCSI can easily be used in routine care as a guide in patient-tailored treatment.

***Acknowledgements*:**
We are indebted to dr. F. van den Elshout (pulmonologist, Rijnstate Hospital, Arnhem) and dr. R. Bunnik (pulmonologist, Maas Hospital, Boxmeer) for their contribution in the patient recruitment and the multidisciplinary Taskforce Assessment of the Department of Pulmonary Rehabilitation for their invaluable contributions to the development of the conceptual models. The study was supported by grants of the Dutch Asthma Foundation, GlaxoSmithKline, Stichting Astmabestrijding, and the Department of Medical Psychology and the Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centrer.

REFERENCES

1. Spilker B, Revicki DA. Taxonomy of quality of life. In B. Spilker (Ed.), Quality of life and pharmaeconomics in clinical trials (2nd ed., pp. 25-31). Philadelphia: Lippincott-Raven Publishers. 1996.
2. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. The Journal of American Medical Association. 1995: 273:59-65.
3. Curtis JR, Patrick DL. The assessment of Health Status among patients with COPD. Journal of European Respiratory. 2003: 41(Supplement):36s-45s.
4. Jones PW, Quirk FH, Baveystock CM. Why quality of life measures should be used in the treatment of patients with respiratory illness. Monaldi Archives for Chest Disease. 1994: 49:79-82.
5. Jones PW. Health Status measurement in chronic obstructive pulmonary disease. Thorax. 2001: 56:880-887.
6. Vercoulen JH, Daudey L, Molema J, Vos P, Peters J, Top M, Folgering H. An Integral Assessment Framework of Health Status in Chronic Obstructive Pulmonary Disease (COPD). International Journal of Behavioral Medicine. 2008: 15(4):263-279.
7. Bowling, A. Health-related quality of life: Conceptual meaning, use and measurement. In Measuring Disease: A review of disease-specific quality of life measurement scales. (Second ed., pp. 1-22). Buckingham - Philadelphia: Open University Press. 2001
8. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American Journal of Respiratory and Critical Care Medicine. 2007: 176(6):532-555.
9. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, De Vet HC. Quality criteria were proposed for measurement properties of Health Status questionnaires. Journal of Clinical Epidemiologie. 2007: 60(1):34-42.
10. Ogden J. Theory and measurement: conceptualisation, operationalisation, and the example of Health Status. In A.Vingerhoets (Ed.), Assessment in Behavioral Medicine (pp. 73-90). East Sussex: Brunner-Routledge. 2001.
11. Celli BR. ATS standards for the optimal management of chronic obstructive pulmonary disease. Respirology. 1997: 2 Supplement 1:S1-S4.
12. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS, Rees J. Optimal assessment and management of chronic obstructive

pulmonary disease (COPD). The European Respiratory Society Task Force. European Respiratory Journal. 1995: 8:1398-1420.
13. Taillefer M, Dupuis G, Roberge M, Le May S. Health-related quality of life models: Systematic review of the literature. Social Indicators Research. 2003: 64:293-323.
14. Verhage TL, Heijdra YF, Molema J, Daudey L, Dekhuijzen PNR, Vercoulen JH. Adequate Patient characterization in COPD: Reasons to go beyond GOLD classification. Open Respiratory Medicine Journal. 2009: 3:1-9.
15. Van Der Molen T, Willemse BW, Schokker S, Ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and Quality of Life Outcomes. 2003: 1:13.
16. Jacobs JE, Maille AR, Akkermans RP, Van Weel C, Grol RPTM. Assessing the quality of life of adults with chronic respiratory diseases in routine primary care: Construction and first validation of the 10-Item Respiratory Illness Questionnaire-monitoring 10 (RIQ-MON10). Quality of Life Research. 2004: 13:1117-1127.
17. EuroQol-a new facility for the measurement of health-related quality of life. The EuroQol Group Health Policy. 1990: 16:199-208.
18. Stel HF, Maille AR, Colland VT, Everaerd W. Interpretation of change and longitudinal validity of the quality of life for respiratory illness questionnaire (QoLRIQ) in inpatient pulmonary rehabilitation. Quality of Life Research. 2003: 12:133-145.
19. Wiebe JS, Penley JA. A psychometric comparison of the Beck Depression Inventory-II in English and Spanish. Psychological Assessment. 2005: 17:481-485.
20. Maillé AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA. The development of the 'Quality-of-Life for Respiratory Illness Questionnaire (QOL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91:297-309.
21. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
22. Vercoulen, JHMM, Bazelmans E, Swanink CMA, Fennis JFM, Galama JMD, Jongen PJH, Hommes OR, van der Meer JWM, Bleijenberg G. Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. Journal of Psychiatric Research. 1997: 31:661-673.
23. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a Health Status measure. Medical Care. 1981: 19:787-805.
24. Jacobs HM, Luttik A, Touw-Otten FWMM, De Melker RA. De 'sickness impact profile' ; resultaten van een valideringsonderzoek van de Nederlandse versie. Nederlands Tijdschrift voor Geneeskunde. 1990: 134:1950-1954.
25. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour Research and Therapy. 1997: 35:785-791.
26. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. Journal of Personality Assessment. 1985: 49:71-75.
27. Arrindell WA, Ettema JHM. SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator. Lisse: Swets & Zeitlinger. 1986.



CHAPTER 4

Health status in COPD cannot be measured with the St. George's Respiratory Questionnaire alone: an evaluation of the underlying concepts of this questionnaire

Leonie Daudey
Jeannette B Peters
Johan Molema
P N Richard Dekhuijzen
Judith B Prins
Yvonne F Heijdra
Jan H Vercoulen

Respiratory Research. 2010: 11:98

ABSTRACT

Background

Improving patients' health status is one of the major goals in COPD treatment. Questionnaires could facilitate the guidance of patient-tailored disease management by exploring which aspects of health status are problematic, and which aspects are not. Health status consists of four main domains (physiological functioning, symptoms, functional impairment, and quality of life), and at least sixteen sub-domains. A prerequisite for patient-tailored treatment is a detailed assessment of all these sub-domains. Most questionnaires developed to measure health status consist of one or a few subscales and measure merely some aspects of health status. The question then rises which aspects of health status are measured by these instruments, and which aspects are not covered. As it is one of the most frequently used questionnaires in COPD, we evaluated which aspects of health status are measured and which aspects are not measured by the St George's Respiratory Questionnaire (SGRQ).

Methods

One hundred and forty-six outpatients with COPD participated. Correlations were calculated between the three sections of the SGRQ and ten sub-domains of the Nijmegen Integral Assessment Framework, covering Symptoms, Functional Impairment, and Quality of Life. As the SGRQ was not expected to measure physiological functioning, we did not include this main domain in the statistical analyses. Pearson's r ≥0.70 was used as criterion for conceptual similarity.

Results

The SGRQ sections *Symptoms* and *Total* showed conceptual similarity with the sub-domain Subjective Symptoms (main domain Symptoms). The sections *Activity, Impacts* and *Total* were conceptual similar to Subjective Impairment (main domain Functional Impairment). The SGRQ sections were not conceptual similar to other sub-domains of Symptoms, Functional Impairment, nor to any sub-domain of Quality of Life.

Conclusions

The SGRQ could facilitate the guidance of disease management in COPD only partially. The SGRQ is appropriate only for measuring problems in the sub-domains Subjective Symptoms and Subjective Impairment, and not for measuring problems in other sub-domains of health status, such as Quality of Life.

BACKGROUND

COPD is a chronic and debilitating disease and a leading cause of morbidity and mortality worldwide [1]. According to the latest estimates of the World Health Organization (WHO), 210 million people have COPD and 3 million people died of COPD in 2005 [2]. Improving patients' health status is one of the major goals in COPD treatment [3].

Quality of life has become an important endpoint in medical care, but still there is no consensus on the definition of these concepts [4]. Smith and colleagues (1999) consider quality of life and health status to be separate constructs, in which quality of life is more related to mental health, whereas health status is more related to physical functioning [4]. The WHO uses a broader definition of health status, by defining health status as 'a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity'. Similarly, others [5,6] define health status as an overall concept covering physiological functioning, symptoms, functional impairment, quality of life, and social functioning as important main domains. These main domains were empirically found to be further divided into sixteen sub-domains [7,8], each sub-domain representing a unique aspect of health status. Despite differences in definitions found in the literature it has become clear that a patient's functioning consists of many conceptually distinct sub-domains. Patient-tailored treatment then requires assessment of all these sub-domains.

Questionnaires could facilitate the guidance of patient-tailored disease management by exploring which aspects of health status are problematic and which aspects are not. The past decade many questionnaires have been developed to measure health status. However, most of these instruments consists of only one or a few subscales and thus measure merely some aspects of health status. The question then rises which aspects of health status are measured by these instruments, and which aspects are not covered.

The St George's Respiratory Questionnaire (SGRQ), for instance, is one of the most frequently used and translated disease specific health status instruments in COPD [9-11]. A recent Pubmed search gave 555 hits (date 06/03/2010; terms SGRQ and St George's Respiratory Questionnaire). The SGRQ has been developed to allow comparative measurement of health between patient populations and to quantify changes in health following therapy [12]. The SGRQ consists of three sections and a total score: *Symptoms*, measuring the frequency and severity of respiratory symptoms; *Activity*, measuring limitation of activities by breathlessness and activities that cause breathlessness; *Impacts*, measuring disturbances in social and psychological functioning due to airway disease; *Total* score summarizes the impact of the disease on overall health status [12-14]. The SGRQ thus measures maximally three of the sixteen aspects of health status. It is not clear which aspects of health status are measured, and which aspects of health status are not measured by the SGRQ. This question is all the important to unravel, because the SGRQ, as many other questionnaires, is subject to conceptual confusion. The SGRQ initially was conceived as a standardized self-completed questionnaire for measuring health and perceived well-being ('QoL') in airways diseases [12]. In the literature, however, the SGRQ is interchangeably

referred to as a measure of quality of life [15], health-related quality of life [16], health status [17], a measure for impaired health [18], or a measure of overall impact of the disease [19]. Different terms are used for the concept(s) the SGRQ measures. Additionally, since the SGRQ is often used as a criterion in validity testing of other instruments [20,21], it is essential to clarify which aspects of health status the SGRQ measures.

In the present study, we tested which aspects of health status are measured by the SGRQ in COPD, by comparing the SGRQ sections *Symptoms, Activity* and *Impact* with multiple aspects of the health status domains symptoms, functional impairment and Quality of Life.

MATERIAL AND METHODS

Subjects

The 146 subjects took part on a longitudinal study on health status in COPD. Patients were recruited from three different outpatient centres in the Netherlands: Radboud University Nijmegen Medical Centre, Maas Hospital Boxmeer, and Rijnstate Hospital Arnhem. Patients had to fulfil the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of a post-bronchodilator FEV_1% predicted between 30 and 80 percent with a reversibility of obstruction of less than 12% [1]. Patients suffering from primary co-morbidity or co-morbidity that prevented full adherence to the research protocol were excluded, as well as patients with an acute exacerbation, recent (<6 months) participation in a rehabilitation program, or who were not able to speak or read Dutch. One-hundred-and-sixty-eight patients participated in this study. After one year, the assessments were repeated in 146 patients (87% of included patients in first part). Reasons for dropout were diverse: passed away (N=5), co-morbidity (N=3), participation in a rehabilitation programme between the first and second assessments (N=2), being too busy (N=4), found participation too exhausting (N=3), or no transportation (N=2). For three patients the reasons for dropout were unknown. Data of these 146 patients were used in the present study. The inclusion procedure is described in detail elsewhere [7]. The study was approved by the Medical Ethics Committee CMO region Arnhem-Nijmegen (P02.1411L; CMO-nr 2002/047). Subjects gave informed consent.

Procedures

Subjects visited the Department of Pulmonary Diseases twice. Physiological assessments were performed and subjects received the Aktometer (accelerometer measuring actual physical activity) [22]. Two weeks later subjects completed questionnaires by the TestOrganiser, a computer program developed by the Department of Medical Psychology and the Department of Instrumental Services of the Radboud University Nijmegen Medical Centre [7]. Questionnaires were presented in the same layout as the paper-and-pencil

versions, and a simple response board enabled subjects with no prior computer experience to operate the TestOrganiser easily.

Measurements

Demographic data were recorded. Pulmonary function tests were performed, including transfer capacity for carbon monoxide using the Jaeger masterlab-spirometer according to ERS-criteria [23], and indices of body composition (BodyStat 1997).

St George's Respiratory Questionnaire (SGRQ)

The SGRQ consists of 50 items with weighted responses divided in three sections - *Symptoms*, *Activity*, and *Impacts* - and a *Total* score [12-14]. Scores are expressed as percentages of the maximally possible sum of weights. A score of zero represents no health impairment, a score of 100 means maximal health impairment.

Health status main domains symptoms, functional impairment, and Quality of Life

Health status was measured by the Nijmegen Integral Assessment Framework (NIAF) [7]. The NIAF provides a detailed and empirical definition of health status and covers the domains physiological functioning, symptoms, functional impairment, and Quality of Life. These four main domains were found to be subdivided into 15 distinct sub-domains [7,8]. In another study [8], we found that fatigue was an additional sub-domain. Factor analyses were used to identify underlying concepts in the data. Social functioning did not emerge as a separate factor, aspects of social functioning were part of the main domains Quality of Life and functional impairment. The sub-domains are measured by different existing instruments, and for each sub-domain a Sub-domain Total Score (STS) was calculated. As the SGRQ was not expected to measure physiological functioning, in this study we only evaluated the ten sub-domains of the main domains symptoms, functional impairment, and Quality of Life. See Table 1 for definitions of the sub-domains and corresponding instruments**.**

Statistical analyses

The relationships between the sections of the SGRQ and the sub-domains of the NIAF, as well as the intercorrelations of the SGRQ sections, were analyzed by Pearson correlation coefficients. To avoid Type I error due to multiple testing P was set at 0.01. A Pearson's $r \geq 0.70$ was used as criterion for conceptual similarity between the sections of the SGRQ and the sub-domains of the NIAF [24].

RESULTS

Subjects

The study sample could be characterized as predominantly male, low educated, and living with a partner (Table 2). Most subjects were GOLD II/III patients. Some subjects were

Table 1 Main domains Symptoms, Functional Impairment and Quality of Life of the Nijmegen Integral Assessment Framework

Domain/Sub-domain	Definition	Instrument (subscales)
Symptoms		
Subjective Symptoms	The patient's overall burden of pulmonary symptoms	PARS-D: Global Dyspnea Activity, Global Dyspnea Burden, Dyspnea Activity [7]; QoLRiQ: Breathing Problems [33]
Dyspnea Emotions	The level of frustration, depressive feelings, and anxiety a patient experiences when dyspnoeic	DEQ: Frustration, Mood, Anxiety [7]
Expected Dyspnea	The level of dyspnea that a patients expect to experience during specific activities no longer performed	PARS-D: Expected Dyspnea [7]
Fatigue	The level of experienced fatigue	CIS: Subjective fatigue [34]
Functional Impairment		
Actual Physical Activity	The actual physical activity a patient performs during two weeks	Aktometer (electronic accelerometer) [22]
Behavioral Impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP: Body Care & Movement, Home Management, Mobility, Ambulation [35]
Subjective Impairment	The experienced degree of impairment in general, and in social functioning	QoLRiQ: General Activities, Social Activities [33]; Global Impairment [7]; SIP: Social Interaction, Burden [35]
Quality of Life		
General QoL	Mood, anxiety, and the satisfaction of a person with his/her life as a whole	Satisfaction With Life Scale [36] Symptom Check List: Anxiety [37] BDI: Primary Care [38]
HRQoL	Satisfaction related to physiological functioning and the future	Satisfaction Physiological Functioning, Satisfaction Future [7]
Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction Spouse, Satisfaction Social [7]

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

classified in GOLD I or IV, due to normal variation in FEV_1 between the time of the first assessment and second assessment one year later.

Conceptual similarity between sections of the SGRQ and sub-domains of the NIAF

The SGRQ sections were significantly correlated to many health status aspects, however conceptual similarity ($r \geq 0.70$) was only reached for two sub-domains of the NIAF (Table 3).

The SGRQ sections *Symptoms* and *Total* were conceptual similar to the NIAF sub-domain subjective symptoms (main domain symptoms). The SGRQ sections *Activity, Impacts,* and *Total* were conceptually similar to the NIAF sub-domain subjective impairment (main domain functional impairment).

Table 2 Demographic, clinical characteristics, and data of the St George's Respiratory Questionnaire of participating COPD patients

Variable		Mean ±SD
Male sex %		76.7
Age (years)		65.8 ±9.0
Education %	Low	48.6
	Middle	29.5
	High	19.9
Personal situation %	Partner	77.8
	Divorced	6.3
	Widowhood	8.3
	Single	7.6
Cigarette smoking %	Current	41.8
	Former	45.9
	Never	11.0
BMI (kg/m^2)		25.9 ±4.1
FEV_1 (L)		1.6 ±0.5
FEV_1 % predicted		53.6 ±13.9
FEV_1/FVC %		44.0 ±11.4
TLC % predicted		103.7±14.6
RV % predicted		128.3 ±30.3
TLCO % predicted		62.3 ±21.5
GOLD %	I	2.1
	II	58.9
	III	34.2
	IV	4.8
SGRQ section	Symptoms	40.9 ±24.8
	Activity	40.9 ±21.8
	Impacts	20.2 ±13.5
	Total	30.2 ±15.4

Data are presented as mean ±SD unless otherwise indicated. Percentages may not add up to 100 due to missing data (three patients with no specified education, two patients with no specified smoking habits). BMI, body mass index; FEV_1, forced expiratory volume in one second; % predicted, as percentage predicted; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; TLCO, transfer capacity (of lung) for carbon monoxide; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SGRQ, St George's Respiratory Questionnaire.

Table 3 Correlations between the St George's Respiratory Questionnaire and the Nijmegen Integral Assessment Framework[#]

		Sections of the St George's Respiratory Questionnaire			
		Symptoms	Activity	Impacts	Total
Main domains of the Nijmegen Integrall Assessment Framework	**Symptoms**				
	Subjective Symptoms	0.70[¶]	0.64	0.60	0.74[¶]
	Dyspnea Emotions	0.25	0.31	0.32	0.35
	Expected Dyspnea	0.43	0.59	0.43	0.57
	Fatigue	0.47	0.57	0.60	0.65
	Functional Impairment				
	Actual Physical Activity	---	0.42	0.31	0.34
	Behavioral Impairment	0.28	0.65	0.54	0.61
	Subjective Impairment	0.67	0.70[¶]	0.71[¶]	0.81[¶]
	Quality of Life				
	General QoL	0.50	0.46	0.52	0.57
	HRQoL	0.43	0.42	0.46	0.51
	Satisfaction Relations	0.24	---	---	0.21

[#]only significant correlations (p<0.01) are shown; [¶]Pearson's r≥0.70 (criterion for conceptual similarity)

Table 4 Intercorrelations between sections of the St George's Respiratory Questionnaire[#]

St George's Respiratory Questionnaire				
	Symptoms	Activity	Impacts	Total
Symptoms	1.00	--	--	--
Activity	0.50	1.00	--	--
Impacts	0.54	0.69	1.00	--
Total	0.73[¶]	0.88[¶]	0.91[¶]	1.00

[#]only significant correlations (p<0.01) are shown; [¶]Pearson's r≥0.70 (criterion for conceptual similarity)

Intercorrelations of the SGRQ sections

Intercorrelations between the SGRQ sections were moderate to high (Table 4). The SGRQ section *Total* exceeded the criterion of conceptual similarity with all SGRQ sections ($r \geq 0.70$, $p<0.01$). The correlation between the sections *Impacts* and *Activity* almost reached the criterion of conceptual similarity ($r = 0.69$, $p<0.01$).

DISCUSSION

The present study evaluated which aspects of health status are measured by the sections of the SGRQ, and which aspects of health status are not covered by the SGRQ. The sections of the SGRQ correlated significantly with most sub-domains of the NIAF, indicating that the SGRQ was related to many health status aspects. However, most correlations were low to moderate and well below 0.70, indicating that shared variance was too low to conclude that sections of the SGRQ were conceptually similar to these sub-domains.

Applying the criterion of conceptual similarity, the SGRQ measured two of the ten evaluated sub-domains of health status. The SGRQ sections *Symptoms* and *Total* showed conceptual similarity with the sub-domain subjective symptoms (main domain symptoms), the SGRQ sections *Activity, Impacts,* and *Total* showed conceptual similarity with the sub-domain subjective impairment (main domain functional impairment).

In a previous study [7] we found a high correlation between the sub-domains subjective impairment and subjective symptoms. The instruments included in these sub-domains were different with respect to the content of the items, but had in common that the item-and-response format required highly subjective and general interpretations by the patient. It was argued that both sub-domains measured highly subjective notions of 'being ill', also referred to as illness perceptions [25]. As the SGRQ reached the criterion for conceptual similarity with these two sub-domains, this would imply that the SGRQ in fact measures illness perceptions, related to symptoms (section *Symptoms* and *Total*) and functional impairment (sections *Activity* and *Impacts*). This conclusion is underlined by the high intercorrelations between the SGRQ sections, some correlations even exceeding the criterion for conceptual similarity.

Although illness perceptions related to symptoms and functional impairment are very relevant concepts, many other important aspects of health status are not covered by the SGRQ. With respect to the SGRQ as a measure of aspects of symptoms, these are restricted to the subjectively experienced severity of pulmonary symptoms. Other important aspects of symptoms, such as dyspnea-related emotions, are not measured specifically. With respect to functional impairment, only the subjectively experienced impairments are measured by the SGRQ. Impairment on the behavioral level or actual physical activity level is not measured by the SGRQ sections. Furthermore, the present study showed that the SGRQ does not measure any of the three sub-domains of quality of life evaluated in this study (general Quality of Life, health-related Quality of Life, and satisfaction relations). Finally, since the SGRQ measures merely two sub-domains of the ten evaluated sub-domains, the SGRQ does not provide a detailed measurement of health status. Similarly, present data show that the SGRQ should be considered a valid measure of impaired health in COPD, as the SGRQ originally was conceived. However, the SGRQ measures only two aspects of impaired health (subjective symptoms and subjective impairment). To measure all aspects of impaired health, and thereby allowing patient-tailored treatment, other instruments need to be included as well.

Some methodological issues need to be addressed. First, the NIAF is not the definite answer to the problem of conceptual confusion in current health status instruments. Other aspects of health status not included in the framework may be relevant to COPD patients. This needs to be addressed in future studies, in which patient feedback should be incorporated. Nevertheless, this framework does provide a much more detailed definition of health status, as expressed by the many sub-domains, and is much more formulated in terms of empirical observations than found in the literature. Each sub-domain represents a (conceptually) unique health status aspect. At least 16 sub-domains are measured to provide a detailed picture of the health status of a COPD patient.

Second, using the criterion of conceptual similarity ($r \geq 0.70$) as a standard for validity seems a very strict criterion. However, considering the conceptual confusion in health status, one must be carefully interpreting results of earlier validity studies. Often, much lower correlations are accepted as evidence for the validity of the instrument under scrutiny. For example, a correlation between two instruments of 0.40 may be statistically significant, but it indicates only 16% of shared variance. Unambiguous conclusions concerning conceptual similarity between two instruments can only be drawn from the results using a strict approach.

The present study focuses on the relationships between the SGRQ sections and the main domains symptoms, functional impairment, and Quality of Life. Therefore, the conclusions of the present study are not applicable with respect to physiological functioning. However, from a theoretical point of view it is unlikely that a questionnaire will provide a direct measure of physiological processes. For example, studies to date [26,27] often show a relationship between FEV1 and the SGRQ. However, these correlations are low to moderate and do not exceed the criterion of conceptual similarity.

With respect to generalizability of the present study, we believe that the present sample may be an adequate reflection of a the Dutch population of patients with COPD seen in an outpatient clinic. This sample may however not be representative for subgroups of COPD such as patients in pulmonary rehabilitation or patients with primary co-morbidity, which were two major exclusion criteria.

An important clinical implication of the present study is that the SGRQ could facilitate the guidance of disease management only partially. The SGRQ can only be used appropriately for exploring problems in the sub-domains subjective symptoms and subjective impairment, and not for exploring problems in other sub-domains of health status, such as aspects of quality of life.

Most instruments claiming to measure specific aspects of health status contain only two to five subscales. Thus, at best only some aspects of health status are measured by a specific instrument. This not only has implications for clinical practice, but also for research purposes. In pharmacological trials, the drug under study may have beneficial effects on some aspects of health status, but not on other aspects. If the instruments used measure only few aspects of health status beneficial effects may be missed. With respect to the use of instruments in clinical practice, the present results indicate that one single instrument cannot provide sufficient information on a patient's health status to effectively tailor treatment to the needs of the individual patient, since measuring all aspects of health status is a prerequisite for patient-tailored treatment. This requires combining different instruments into a battery of instruments measuring multiple aspects of health status. However, implementing instruments in daily practice to facilitate disease management requires that instruments are not too time consuming. The past decade a few short instruments have been developed specifically to allow measurement of health status aspects in routine care, such as the Clinical COPD Questionnaire [28], the Respiratory Illness Questionnaire-monitoring 10 [29], and the EuroQoL [30]. None of these instruments provide

a detailed picture of a patient's health status. Recently, we developed the Nijmegen Clinical Screening Instrument (NCSI), an instrument which can be used in routine care [31]. The NCSI is based on the NIAF and measures eleven sub-domains of physiological functioning, symptoms, functional impairment, and quality of life. The NCSI thus enables a quick (15-25 minutes) and detailed assessment of health status. Also, the COPD Assessment Test (CAT) was developed [31], 'a validated short and simple instrument for assessing the impact of COPD on health status'. The CAT is constructed as a uni-dimensional instrument, i.e. measuring one single concept, as expressed in a single score. In addition, the correlation between the CAT and the SGRQ-C was well above the criterion for conceptual similarity (r=0.80) [30]. Taken together, it is very likely that the CAT, like the SGRQ, measures illness perceptions. How important illness perceptions may be, patient-tailored treatment requires a detailed assessment of many aspects of health status. Therefore, the CAT also will have limited value in patient-tailored treatment.

CONCLUSIONS

Detailed measurement of health status in patients with COPD is a prerequisite for patient-tailored treatment. However, carefulness should be noted when selecting instruments to measure health status, because most instruments measure only a few aspects of health status. The SGRQ can only be used appropriately for measuring problems in the sub-domains Subjective Symptoms and Subjective Impairment, and not for measuring problems in other sub-domains of health status, such as aspects of Quality of Life. Different instruments should be combined to provide a detailed picture of a patient's health status.

Acknowledgements

We are indebted to Dr. F. van den Elshout (pulmonologist, Rijnstate Hospital, Arnhem) and Dr. R. Bunnik (pulmonologist, Maas Hospital, Boxmeer) for their contribution in the patient recruitment and the multidisciplinary Taskforce Assessment of the Department of Pulmonary Rehabilitation for their invaluable contributions to the development of the conceptual models.

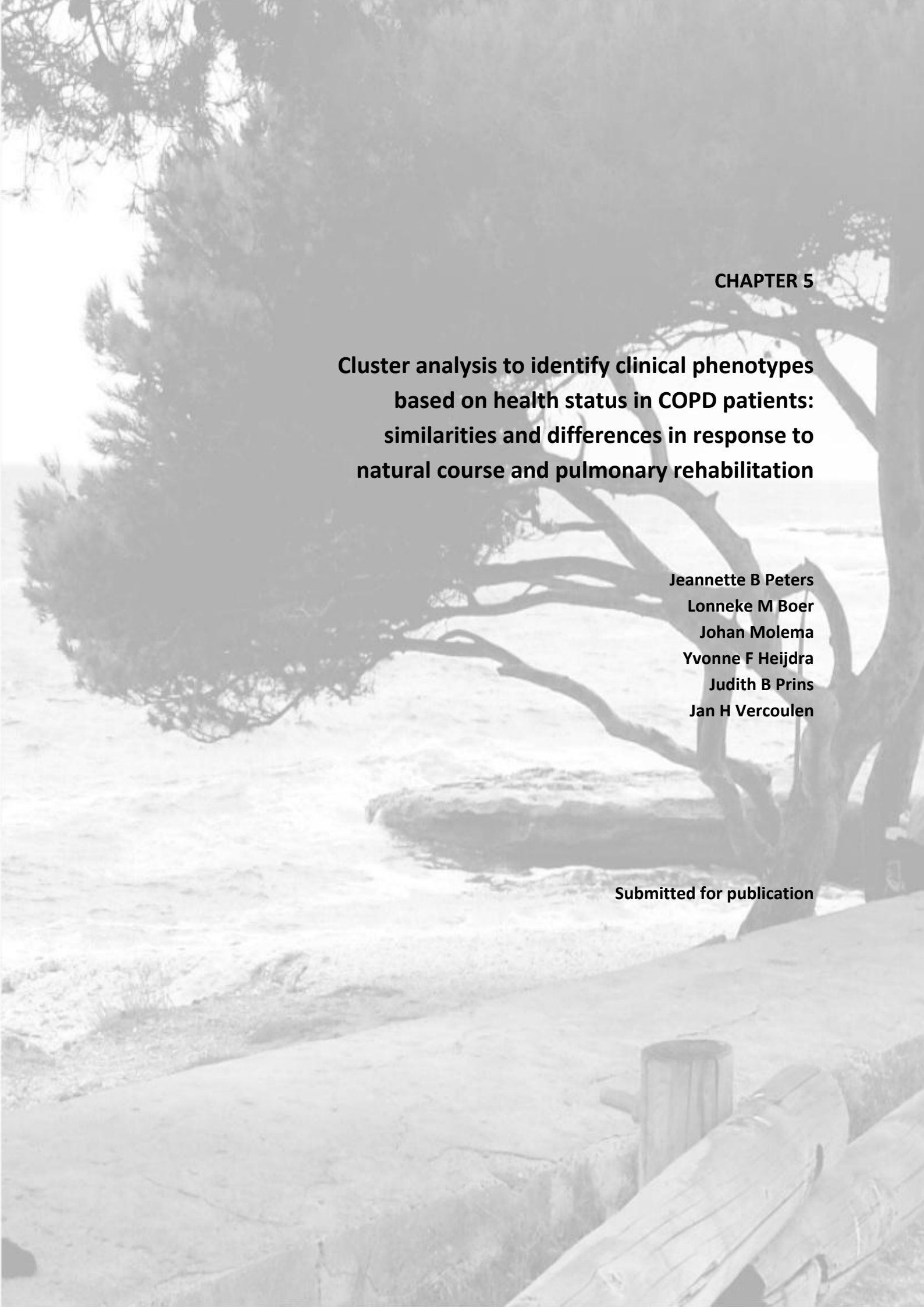
The study was supported by grants of the Dutch Asthma Foundation and GlaxoSmithKline.

REFERENCES

1. Celli BR, MacNee W: Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. European Respiratory Journal 2004: 23:932-946.
2. World Health Organisation [http://www.who.int/respiratory/copd/en/]
3. Workshop Report: Global Strategy for Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease - Update 2009.
4. Smith KW, Avis NE, Assmann SF: Distinguishing between quality of life and health status in quality of life research: a meta-analysis. Quality of Life Research. 1999: 8:447-459.
5. Wilson IB, Cleary PD: Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Journal of the Americain Medical Association. 1995, 273:59-65.
6. Taillefer M, Dupuis G, Roberge M, Le May S: Health-related quality of life models: Systematic review of the literature. Social Indicators Research. 2003: 64:293-323.
7. Vercoulen JH, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H: An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavioral Medicine. 2008: 15:263-279.
8. Peters JB, Heijdra YF, Daudey L, Molema J, Dekhuijzen PNR, Vercoulen JH: Prevalence and severity of fatigue and its relationships with dyspnea and health status in COPD patients [abstract]. American Journal of Respiratory and Critical Care Medicine. 2007: 175:A642
9. Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW: American translation, modification, and validation of the St. George's Respiratory Questionnaire. Clinical Therapy. 2000: 22:1121-1145.
10. Chan SL, Chan-Yeung MM, Ooi GC, Lam CL, Cheung TF, Lam WK, Tsang KW: Validation of the Hong Kong Chinese version of the St. George Respiratory Questionnaire in patients with bronchiectasis. Chest. 2002: 122:2030-2037.
11. Bourbeau J, Maltais F, Rouleau M, Guimont C: French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. Canadian Respiratory Journal. 2004: 11:480-486.
12. Jones PW, Quirk FH, Baveystock CM: The St George Respiratory Questionnaire. Respiratory Medicine. 1991, 85:25-31.
13. Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. American Review of Respiratory Disease. 1992: 145:1321-1327.
14. Jones PW, Spencer S, Adie S: The St George's Respiratory Questionnaire Manual. London: 2003.
15. Okubadejo AA, Paul EA, Jones PW, Wedzicha JA: Does long-term oxygen therapy affect quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia? European Respiratory Journal. 1996: 9:2335-2339.
16. Nishiyama O, Taniguchi H, Kondoh Y, Nishimura K, Suzuki R, Takagi K, Yamaki K: The effectiveness of the visual analogue scale 8 in measuring health-related quality of life for COPD patients. Respiratory Medicine. 2000: 94:1192-1199.
17. Vestbo J, Soriano JB, Anderson JA, Calverley P, Pauwels R, Jones P: Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD. Respiratory Medicine. 2004: 98:1045-1050.

18. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R: Validation of the St. George's Respiratory Questionnaire in bronchiectasis. American Journal of Respiratory and Critical Care Medicine. 1997: 156:536-541.
19. Jones PW: Health status measurement in chronic obstructive pulmonary disease. Thorax. 2001: 56:880-887.
20. Stallberg B, Nokela M, Ehrs PO, Hjemdahl P, Wikstrom JE: Validation of the Clinical COPD Questionnaire in primary care. Health and Quality of Life Outcomes. 2009: 7:26.
21. Camelier A, Rosa FW, Jones PW, Jardim JR: Brazilian version of airways questionnaire 20: a reproducibility study and correlations in patients with COPD. Respiratory Medicine. 2005: 99:602-608.
22. Gibson PG, Talbot PI, Toneguzzi RC: Self-management, autonomy, and quality of life in asthma. Population Medicine Group 91C. Chest. 1995: 107:1003-1008.
23. Tammeling GJ, Quanjer PH: Standardized lung function testing. European Respiratory Journal. 1993: 6:5-33.
24. Ogden J: Theory and measurement: conceptualisation, operationalisation, and the example of health status. In Assessment in Behavioral Medicine. Edited by Edited by Vingerhoets A. East Sussex: Brunner-Routledge: 2001:73-90.
25. Scharloo M, Kaptein AA, Weinman J, Hazes JM, Willems LN, Bergman W, Rooijmans HG: Illness perceptions, coping and functioning in patients with rheumatoid arthritis, chronic obstructive pulmonary disease and psoriasis. Journal of Psychosomatic Research. 1998: 44:573-585.
26. Madueno A, Martin A, Peculo JA, Anton E, Paravisini A, Leon A: Usefulness of inspiratory capacity measurement in COPD patients in the primary care setting. International Journal of General Medicine. 2009: 2:219-225.
27. Pereira ED, Pinto R, Alcantara M, Medeiros M, Mota RM: Influence of respiratory function parameters on the quality of life of COPD patients. Journal of Brasilian Pneumology. 2009: 35:730-736.
28. Van Der Molen T, Willemse BW, Schokker S, Ten Hacken NH, Postma DS, Juniper EF: Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and Quality of Life Outcomes. 2003: 1:13.
29. Jacobs JE, Maille AR, Akkermans RP, van Weel C., Grol RPTM: Assessing the quality of life of adults with chronic respiratory diseases in routine primary care: Construction and first validation of the 10-Item Respiratory Illness Questionnaire-monitoring 10 (RIQ-MON10). Quality of Life Research. 2004: 13:1117-1127.
30. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990: 16:199-208.
31. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH: Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. Quality of Life Research. 2009: 18:901-912.
32. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline LN: Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009: 34:648-654.
33. Maillé AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA: The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QOL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91:297-309.

34. Vercoulen JHMM, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G: Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
35. Vercoulen JHMM, Bazelmans E, Swanink CMA, Fennis JFM, Galama JMD, Jongen PJH, Hommes OR, van der Meer JWM, Bleijenberg G: Physical activity in chronic fatigue syndrome: assessment and its role in fatigue. Journal of Psychiatric Research. 1997: 31:661-673.
36. Diener E, Emmons RA, Larsen RJ, Griffin S: The satisfaction with life scale. Journal of Personality Assessment. 1985: 49:71-75.
37. Arrindell WA, Ettema JHM: SCL-90: Handleiding bij een multidimensionele psychopathologie-indicator [SCL-90: Manual for a multifaceted measure of psychopathology]. Lisse: Swets & Zeitlinger; 1986.
38. Beck AT, Guth D, Steer RA, Ball R: Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour Research and Therapy. 1997: 35:785-791.



CHAPTER 5

Cluster analysis to identify clinical phenotypes based on health status in COPD patients: similarities and differences in response to natural course and pulmonary rehabilitation

Jeannette B Peters
Lonneke M Boer
Johan Molema
Yvonne F Heijdra
Judith B Prins
Jan H Vercoulen

Submitted for publication

ABSTRACT

Background

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease. Not only the (extra-)pulmonary manifestations, but also the impact on health status differs between patients. Some patients experience more symptoms, functional impairment, and lower quality of life (QoL) than would be expected based on the physiological disease severity. In other patients, these domains of health status are better balanced. Adaptation to the disease, reached by adequate self-management behaviour, plays a role in this. The primary aim of this study was to identify clinical phenotypes based on health status and examine whether these are an expression of level of adaptation. The secondary aim was to examine whether these clinical phenotypes show a different response in health status in usual care and in an inpatient pulmonary rehabilitation program (PR).

Methods

A cluster analysis was performed on baseline data of health status in 160 outpatients. Based on a discriminant analysis PR patients were assigned to one of the identified clusters. With paired t-tests the effect of usual care (n=143) and effect of PR (n= 459) on health status in the clusters was examined.

Results

Three phenotypes were identified that were based on the balance or imbalance between symptoms, impairments and QoL versus physiological disease severity. Two types were adapted: phenotype 1 ‘moderate COPD - low impact on health status’ and phenotype 3 ‘severe COPD - moderate impact on health status’. One type was not-adapted: phenotype 2 ‘moderate COPD - high impact on health status’. In usual care the health status of the patients remained unchanged over a one year period. At the end of inpatient pulmonary rehabilitation program (PR) significant improvements were found on four (phenotype 1) to ten (phenotype 2) of eleven sub-domains of health status. These improvements resulted in a better balance between the four domains of health status, indicating better adaptation.

Conclusions

Three clinical phenotypes were identified based on health status, that differed in the level of adaptation and response to treatment. Knowing to which clinical phenotype a patient belongs can help to optimize patient-tailored treatment.

BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1]. The various pulmonary and extra-pulmonary manifestations of COPD make it a complex and heterogeneous disorder [2]. In the past years, the acknowledgement of the heterogeneity of COPD has led to an increasing number of studies attempting to identify homogeneous subgroups. The hypothesis of these studies is that each subgroup responds differently to (pharmacological) treatment and has a different course in time. Identification of phenotypes would enhance patient tailored treatment and improve outcome [3-5].

To date, most studies focused on identification of phenotypes based mainly, and sometimes exclusively, on the (patho)physiological disease characteristics of COPD [6-10]. However, patients with COPD not only have physiological disturbances, but also may experience symptoms, functional impairments, and a lowered quality of life. From this perspective health status can be defined as comprising of four main domains: physiological functioning, symptoms, functional impairments, and quality of life [11]. These main domains have been shown to be subdivided into many more concrete sub-domains, each representing unique information of a patient's health status [12]. The main domains symptoms, functional impairments, and quality of life have been shown to be poorly related to pathophysiological aspects and the physiological functioning [2, 12, 13]. This can be observed in clinical practice where some patients report more severe symptoms, functional impairments, or lower quality of life than is expected based on physiological test results, and vice versa.

Symptoms, functional impairments, and quality of life are not solely determined by physiological functioning, but also by the degree to which the patient succeeds to adapt to the illness through adequate self-management behaviours [14-16]. Examples of self-management strategies are: adherence to medication regimes, exacerbation management, adopting a healthy life style (stop smoking, regular exercising), energy saving strategies, breathing regulation, and stress management. Adopting self-management strategies by the patient will result in better adaptation to the disease and subsequently the patient will experience less impact on health status. However, adequate adaptation requires behaviour change by the patient [14, 15]. Not all patients succeed to change behaviour and as a result may suffer from more severe symptoms, functional impairments, and lower quality of life than would be expected based on physiological functioning. Identification of clinical phenotypes reflecting the degree of adaptation to the disease could be of added value in addition to pathophysiological phenotypes in guiding patient-tailored treatment.

In the present study we investigated whether clinical phenotypes can be identified that reflect the level of adaptation to the disease using cluster analysis based on all four domains of health status. We hypothesized that adaptation to the disease is reflected by the

relative balance between disease severity (i.e. physiological functioning) on the one hand and the severity of symptoms, functional impairments and reduced quality of life on the other. In patients who are adapted the four domains of health status are in balance, in patients who are not adapted these four domains are not in balance. Although this balance/imbalance can be observed in clinical practice, such profiles have not yet been identified through empirical studies. Burgel et al. [4] already found that their clinical phenotypes were not based on airflow limitation and showed marked differences in quality of life and symptoms. In the present study we included also parameter measuring functional impairment. The secondary aim was to explore if these clinical phenotypes respond differently to usual care and to a multidisciplinary pulmonary rehabilitation program, which includes an intensive array of interventions aimed at improving adaptation to the disease by teaching the patient adequate self-management strategies in addition to exercise training.

METHODS

We used two different datasets in the present study. For the identification of the clinical phenotypes we used a dataset of stable COPD outpatients receiving usual care at an outpatient clinic (OP group). We expected that in this sample two groups of patients could be identified, those who are adapted to the disease and those patients who are not. In this sample we also investigated the course in time of these phenotypes, over a one-year period.

To investigate response to treatment in the identified phenotypes a sample of patients enrolled in a multidisciplinary pulmonary rehabilitation program was used (PR group). This pulmonary rehabilitation program aims at improving integral health status (i.e. physiological functioning, symptoms, functional impairments, and quality of life) and contains interventions to improve physiological functioning (e.g. exercise training), but also a wide array of interventions to improve the adaptation to the disease by teaching the patient self-management behaviors (e.g. education and specific cognitive behavioral interventions). This program is in line with the recent ATS/ERS statement on pulmonary rehabilitation [17]. We expected that the majority of the patients in this sample could be labelled as non-adapted at the start of the program and would benefit most from the pulmonary rehabilitation program.

Subjects

Outpatients (OP group)

Outpatients with stable COPD were recruited between 2002 and 2005 as part of a longitudinal study on health status in COPD [12] at the University Lung Centre Dekkerswald of the Radboud University Medical Centre, Maas Hospital Boxmeer, and Rijnstate Hospital Arnhem. During one year all patient charts were screened by a pulmonologist, which resulted in 361 eligible patients, of whom 168 (47%) eventually participated. Complete datasets at baseline were present of 160 outpatients. COPD was diagnosed by the presence

of a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of <70% according to the GOLD guidelines [1]. In the present study only patients with an FEV_1% of predicted between 30% and 80% were included. Exclusion criteria were: co morbidity dominating health status, an acute exacerbation, recent participation in pulmonary rehabilitation program (within past 6 months), and inability to completely adhere to the research protocol. A detailed description of the recruitment procedure, the study sample and measurements can be found elsewhere [12]. The study was approved by the local Ethics committee (P02.1411L; CMO-nr2002/047) and informed consent was obtained from all participants.

Pulmonary rehabilitation sample (PR group)

Complete datasets were collected of 459 patients with COPD who completed a 12-week inpatient multidisciplinary pulmonary rehabilitation program at the University Lung Centre Dekkerswald of the Radboud University Medical Centre, between July 2002 and July 2013 as part of usual care. Based on extensive assessments and clinical interviews by seven disciplines (pulmonologist, psychologist, physiotherapist, nurse, dietician, psychomotor therapist, social worker) for each individual patient goals were set for the pulmonary rehabilitation program. During twelve weeks the patients followed a multidisciplinary and individualized treatment program, consisting of a training program, education sessions, group therapy and individual therapy. Every three weeks the treatment progress was evaluated by the seven disciplines and with the patient. If necessary the treatment program was adapted. Exclusion criteria for the present study: inability to speak or read Dutch and/or an incomplete dataset. Data collection was part of usual care and anonimised before analyses.

Data collection

Baseline assessments for both sample were performed during two days in the OP-sample and during three days in the PR-sample. During the first visit a pulmonary function tests, bioelectrical impedance, and maximal incremental cycle ergometry testing were performed. During the second visit data were collected on demographics, tobacco smoking, self-reported co morbidities and health status was measured by the Nijmegen Clinical Screening Instrument (NCSI) [18]. The NCSI is a battery of existing instruments that was empirically composed such that overlap between instruments was avoided and that a wide variety of aspects of integral health status can be measured. The NCSI measures eleven sub-domains of integral health status (See Table 1). For all scores, the higher the score on a sub-domain the more problematic. In the PR-sample, on the second and third day interviews by seven disciplines also took place.

All assessments (except incremental cycle ergometry) were repeated after one year in the OP group (complete datasets of 143 patients) and at the end of the rehabilitation in the PR group (459 complete datasets).

Table 1 Health status sub-domains and their definition and included instruments of the Nijmegen Clinical Screening Instrument (NCSI)

sub-domain	Definition	Instruments/measurement	No of items
Physiological functioning			
Airflow		Post bronchodilator FEV_1% of predicted	
Body Composition		Body Mass Index	
Exercise Capacity		VO_2 max % of predicted	
Symptoms			
Subjective Symptoms	The patient's overall burden of pulmonary symptoms	PARS-D Global Dyspnea Activity [12] PARS-D Global Dyspnea Burden [12]	2
Dyspnoea Emotions	The level of frustration and anxiety a person experiences when dyspnoeic	DEQ Frustration [12] DEQ Anxiety [12]	6
Fatigue	The level of experienced fatigue	CIS Subjective fatigue [20]	8
Functional Impairment			
Subjective Impairment	The experienced degree of impairment in general	QoLRiQ General Activities [21]	4
Behavioral Impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP Home Management [22] SIP Ambulation [22]	22
Quality of Life			
General Quality of Life	Mood and the satisfaction of a person with his/her life as a whole	BDI Primary Care [23] Satisfaction With Life Scale[24]	12
Health-related Quality of Life	Satisfaction related to physical functioning and the future	Satisfaction physiological functioning [12] Satisfaction future [12]	2
Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction spouse [12] Satisfaction social [12]	2

FEV_1: Forced expiratory volume in 1 seconde; VO_2max : maximal oxygen uptake; PARS-D: Physical Activity Rating Scale-Dyspnea; DEQ: Dyspnea Emotions Questionnaire; CIS: Checklist Individual Strength; SIP: Sickness Impact

Statistical methods

Primary aim: Identification of clinical phenotypes in the OP group

To identify clinical phenotypes the hierarchical cluster analysis using Ward's method (with squared Euclidean distance) [4, 19] was performed. Ward's cluster analysis is applied when there is no prior knowledge about the number of clusters or how the clusters may be characterized. In this analysis grouping is based such that subjects in the same cluster are more similar to each other than to subjects in other clusters. The following 11 parameters were included in the Ward's cluster analysis; FEV_1% of predicted, body composition (BMI $kg \cdot m^{-2}$), exercise capacity (VO_2 max% of predicted), subjective symptoms, dyspnea emotions, fatigue, subjective impairment, behavioral impairment, general quality of life, health related quality of life, and satisfaction relations. Based on the dendogram the optimal number of clusters can be identified.

Second, a one-way ANOVA and Tukey's *post hoc* test were performed to determine whether all included variables are significantly different between the clusters.

Third, a (stepwise) discriminant function analysis was performed to determine which parameters are most discriminatory between the clusters. The discriminant cluster analysis also creates an equation, which allows assigning new cases to the clusters. This equation was used to assign each of the 459 patients of the PR group into a cluster.

Secondary aim: Examination of change in health status over time in usual care (OP group) and treatment response (PR group).

To analyse change over time in health status sub-domains in usual care, paired t-tests were performed for each sub-domain in outpatients who completed the assessment one year later (N=143, 89.4%). For each sub-domain the score at baseline was compared to the score after one year (except for exercise capacity, because the maximal ergometry test was not performed during the second assessment). These analyses were performed on the whole OP group and for each cluster separately.

Paired t-tests were performed to examine response to treatment (i.e. improvement in health status) in 459 patients of the PR group. The scores on the 11 outcome measures before rehabilitation were compared to the scores at the end of rehabilitation for the whole group PR group and for each of the clusters separately.

All statistics are presented as mean ± standard deviation (SD) or percentage (number of patients, n). Differences between clusters on sex, GOLD-grade, nutritional status, tobacco use, and education were tested with Pearson chi square test and differences between clusters on age, Tiffeneau index, and number of self-reported co morbidities were analysed with Oneway ANOVA. Z-scores were calculated for allowing comparisons of the different sub-domains and to illustrate the relative distance from the total group mean (Z-score = 0). Z-scores were calculated as: (phenotype mean score - baseline mean score of OP group) / baseline standard deviation of OP group. Differences in usual care and response to treatment were tested with Paired t-tests. To avoid Type I error due to multiple testing P was set at 0.01. All statistics were performed by using SPSS16.0 (SPSS Inc, Chicago, IL.).

RESULTS

Outpatient study sample (OP group)

The baseline characteristics of the OP group are presented in Table 2. Most patients were male, overweight, former smoker, low educated, and 76% reported having one or more co morbidities Due to normal variation in FEV_1 some patients were classified as GOLD grade 1 or GOLD grade 4 (8%).

Table 2 Baseline characteristics of outpatients (N=160); for total group and for each identified phenotype

	Total group	Phenotype 1 (n=53)	Phenotype 2 (n=34)	Phenotype 3 (n=73)	p-value
Male	77 (123)	77.4 (41)	70.6 (24)	79.5 (58)	0.06
Age (mean ±sd)	64.2 ±9.1	65.1 ±9.3	64.5 ±8.4	63.4 ±9.2	0.56
Tiffeneau (FEV_1/FVC)	42.9 ±11.4	46.9 ±9.2	46.2 ±13.0	38.6 ±10.6	
GOLD grade					<0.01
grade 1 (mild)	2.5 (4)	5.7 (3)	3.0 (1)	-	
grade 2 (moderate)	50.3 (80)	73.6 (39)	51.5 (17)	32.9 (24)	
grade 3 (severe)	42.1 (67)	20.8 (11)	42.4 (14)	57.5 (42)	
grade 4 (very severe)	5.0 (8)	-	3.0 (1)	9.6 (7)	
Nutritional status					<0.01
Underweight (BMI <21)	11.9 (19)	7.5 (4)	14.7 (5)	13.7 (10)	
Normal weight (>21 BMI <25)	35.0 (56)	54.7 (29)	11.8 (17)	31.5 (23)	
Overweight (>25 BMI <30)	37.5 (60)	30.2 (16)	50.0 (17)	37.0 (27)	
Obese (BMI >30)	15.6 (25)	7.5 (4)	23.5 (8)	17.8 (13)	
Tobacco use					<0.01
Smoker	26.3 (42)	22.6 (12)	20.6 (7)	31.5 (23)	
Former smoker	60.0 (96)	50.9 (27)	61.8 (21)	65.8 (48)	
Never smoked	13.8 (22)	26.4 (14)	17.6 (6)	2.7 (2)	
Education					0.63
Low	51.6 (82)	50.0 (26)	53.0 (18)	52.0 (38)	
Middle	30.2 (48)	28.58 (15)	23.5 (8)	34.3 (25)	
High	18.2 (29)	21.1 (11)	23.5 (8)	13.7 (10)	
Co morbidities (self-reported)	1.34 ± 1.25	1.25 ±1.00	2.41 ±1.46	0.92 ±1.02	<0.01
None	28.1 (45)	24.5 (13)	5.9 (2)	41.1 (30)	
Fatigue	30.0 (48)	22.6 (12)	70.6 (24)	16.4 (12)	
Back pain	30.6 (49)	32.1 (17)	38.2 (13)	26.0 (19)	
Rheumatoid arthritis	24.4 (39)	15.1 (8)	61.8 (21)	13.7 (10)	
Psychological problems	6.3 (10)	-	26.5 (9)	1 (1)	
Diabetes mellitus	5.0 (8)	7.5 (4)	2.9 (1)	4.1 (3)	
Cancer	3.1 (5)	3.8 (2)	2.9 (1)	2.7 (2)	
Cardiac disease	7.5 (12)	5.7 (3)	14.7 (5)	5.5 (4)	
Other	27.5 (44)	37.7 (20)	23.5 (8)	21.9 (16)	

Data are expressed as % (N) or mean ± SD; FEV_1%: Forced expiratory volume in 1 second; FVC: Forced Vital Capacity; GOLD: global initiative for chronic obstructive lung disease; BMI: body mass index

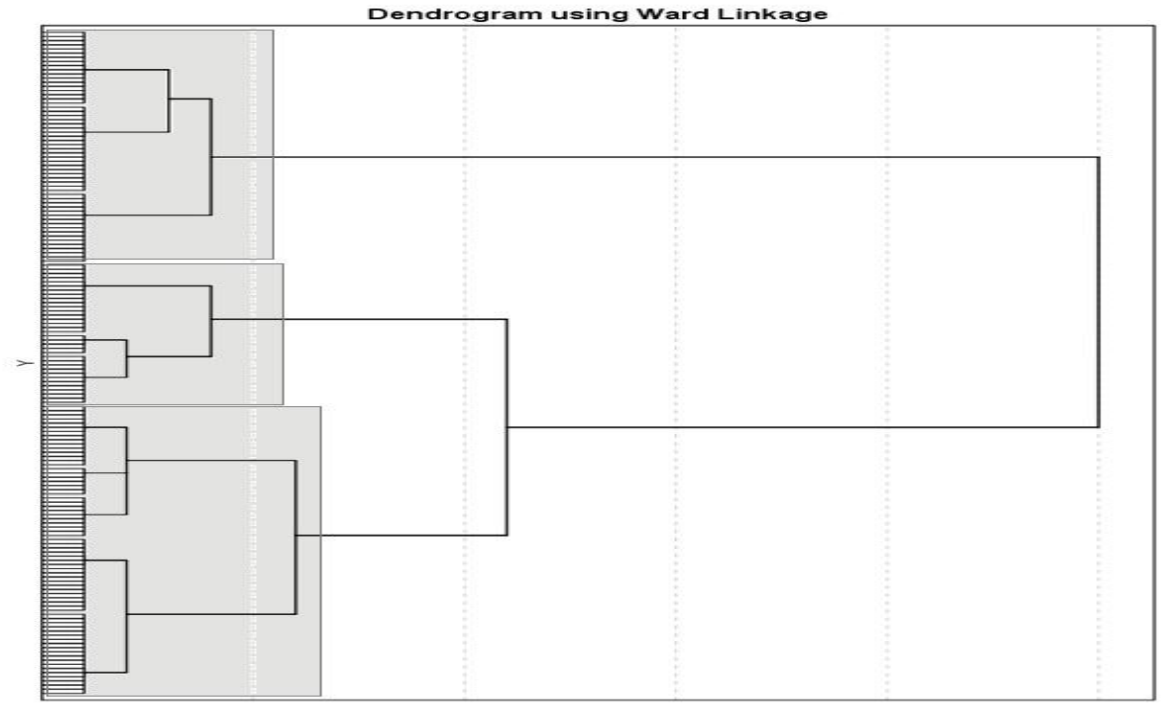


Figure 1 Dendogram showing the results of the Ward's cluster analysis in 160 outpatients with COPD. Note: Each line at the vertical axis represents a patient. Patients who are more similar to each other than to other patients are grouped together. The length of the horizontal lines represents the degree of similarity between the patients in the groups.

Identification of clinical phenotypes in the OP group

The hierarchical cluster analysis using Ward's method on data of 160 patients of the OP group produced three clusters (Figure 1). Significant differences were found on baseline characteristics between the three clusters in BMI categories, tobacco use, and number of self-reported co morbidities (Table 2). The One-way ANOVA Tukey's *post hoc* test showed that the three clusters were significantly different on all included sub-domains, except for body composition (BMI, Table 3).

The first cluster (phenotype 1) was characterized by having moderate COPD, normal weight, high performance on exercise capacity, and mild impact on symptoms, functional impairments, and quality of life (Table 2, Table 3 and Figure 2). Cluster 2 (phenotype 2) patients were characterized by moderate COPD, overweight, moderate performance on exercise capacity, and with high impact on symptoms, impairment, and quality of life. Cluster 3 (phenotype 3) patients were characterized by severe COPD, overweight, moderate performance on exercise capacity, and mild impact on symptoms, impairment, and quality of life.

Although comparable on FEV_1% predicted and BMI with phenotype 1, phenotype 2 patients had significantly higher scores on all sub-domains of symptoms, functional impairment, and quality of life compared to phenotype 1 (Table 3 and Figure 2).

Table 3 Baseline characteristics of 160 outpatients; for total group and each phenotype

	Outpatients (N=160)		phenotype 1 (n=53)	phenotype 2 (n=34)	phenotype 3 (n=73)	Oneway	Tukey's post hoc-tests		
Domain/sub-domain	Mean ±SD	[95% CI]	Mean ±SD	Mean ±SD	Mean ±SD	ANOVA	1 vs 2	1 vs 3	2 vs 3
Physiological Functioning									
FEV_1% of pred	51.7 13.7	[49.6 to 53.9]	59.8 ±11.8	53.4 ±12.0	44.5 ±12.0	**<0.01**	0.04	**<0.01**	**<0.01**
BMI	25.8 ±4.0	[25.1 to 26.4]	24.9 ±3.0	26.6 ±4.5	26.0 ±4.4	0.09	-	-	-
VO_2 max % of predicted	71.9±19.8	[68.9 to 74.8]	91.4 ±13.9	65.8 ±12.6	59.2 ±10.0	**<0.01**	**<0.01**	**<0.01**	0.03
Symptoms									
Subjective Symptoms	7.2 ±4.7	[6.5 to 7.9]	4.5 ±3.5	10.9 ±3.8	7.6 ±4.5	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Dyspnea Emotions	9.8 ±3.2	[9.3 to 10.3]	9.3 ±3.0	11.9 ±3.6	9.1 ±2.7	**<0.01**	**<0.01**	0.87	**<0.01**
Fatigue	27.0 ±11.2	[25.2 to 28.7]	21.2 ±7.7	39.4 ±8.5	25.5 ±9.7	**<0.01**	**<0.01**	0.02	**<0.01**
Functional Impairment									
Subjective Impairment	9.8 ±4.9	[9.0 to 10.5]	6.9 ±2.7	15.3 ±5.0	9.4 ±3.8	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Behavioral Impairment	15.1 ±13.0	[13.1 to 17.2]	7.0 ±6.8	30.0 ±12.2	14.4 ±11.0	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Quality of Life									
General QoL	14.1 ±12.1	[12.2 to 16.0]	9.1 ±5.7	29.4 ±14.4	10.6 ±8.0	**<0.01**	**<0.01**	0.65	**<0.01**
HrQoL	4.1 ±1.7	[3.8 to 4.3]	3.2 ±0.9	5.9 ±1.6	3.9 ±1.5	**<0.01**	**<0.01**	0.02	**<0.01**
Satisfaction Relations	3.1 ±1.4	[2.9 to 3.3]	2.8 ±1.1	4.3 ±1.9	2.8 ±1.0	**<0.01**	**<0.01**	0.98	**<0.01**

Data are expressed as mean ± SD. FEV_1%: Forced expiratory volume in 1 second; BMI: body mass index; p-values in **bold**: significant differences between the phenotypes

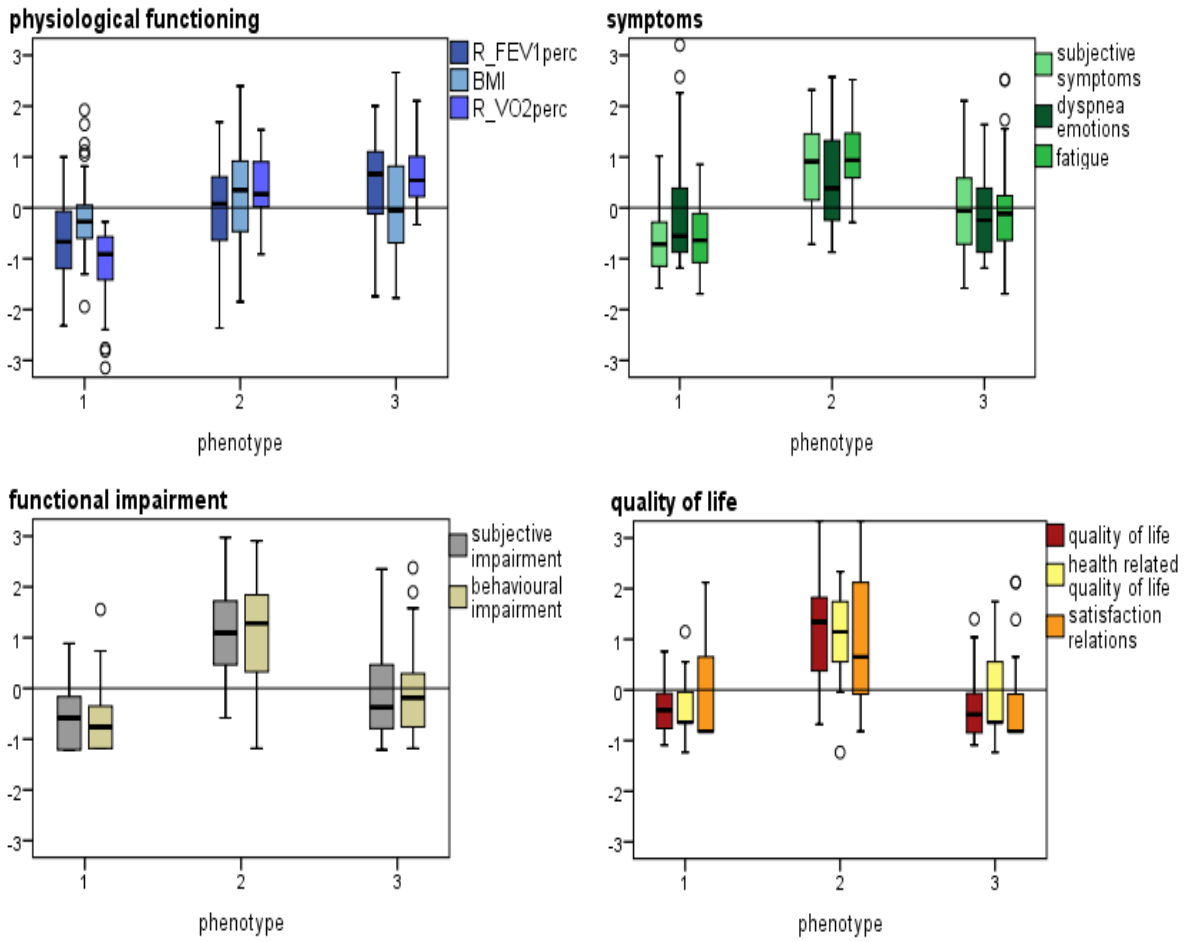


Figure 2 Mean z-scores on the sub-domains for each phenotype.
Note: All scores the higher the more problematic, for this figure the FEV_1% of predicted and VO_2 % max of predicted were mirrored. 1= 'moderate COPD –mild impact on health status'; 2= 'moderate COPD - high impact on health status'; 3= 'severe COPD - mild impact on health status'

Phenotype 3 patients had significantly poorer FEV_1% predicted than phenotype 2, but reported significantly lower impact on symptoms, functional impairment and quality of life when compared to phenotype 2. Remarkably, phenotype 3 had more severe COPD than phenotype 1, but had similar mild impairment in five out of six sub-domains of the main domains symptoms and quality of life ($p > 0.01$).

Discriminant analysis showed that 95% of the OP group could correctly be classified by the following five variables: VO_2% predicted, FEV_1% predicted, general quality of life, behavioral impairments, and fatigue.

Pulmonary rehabilitation study sample (PR group)

Baseline characteristics of the 459 COPD patients of the PR group are presented in table 4. Almost half was female, most had moderate to very severe COPD, were former smoker, low educated, and 72% reported having one or more co morbidities. Based on the equation from the discriminant analysis the patients of the PR group were assigned into one of the three phenotypes. Whereas patients of the OP group primarily were identified as phenotype 1

Table 4 Baseline characteristics of patients who completed pulmonary rehabilitation; for total group and each phenotype

	total group (N=459)	Phenotype 1 (n=27) moderate COPD - mild impact health status	Phenotype 2 (n=271) moderate COPD - high impact health status	Phenotype 3 (n=161) severe COPD - mild impact health status
Male	53.5 (243)	50.0 (13)	46.5 (125)	66.0 (105)
Age	60.5 ±8.8	58.4 ±9.2	60.5 ±8.8	60.8 ±8.8
Tiffeneau (FEV_1/FVC)	36.7 ±12.1	46.8 ±10.9	38.9 ±12.2	31.3 ±9.8
GOLD grades				
grade 1 (mild)	3.8 (17)	12.0 (3)	4.9 (13)	0.6 (1)
grade 2 (moderate)	22.3 (100)	56.0 (14)	26.6 (71)	9.6 (15)
grade 3 (severe)	47.0 (211)	28.0 (7)	48.3 (129)	47.8 (75)
grade 4 (very severe)	26.9 (121)	4.0 (1)	20.2 (54)	42.0 (66)
Nutritional status				
Underweight (BMI <21)	14.7 (67)	18.5 (5)	14.1 (38)	14.9 (24)
Normal weight (>21 BMI <25)	34.6 (158)	40.7 (11)	32.7 (88)	36.6 (59)
Overweight (>25 BMI <30)	32.2 (147)	37.0 (10)	27.5 (74)	39.1 (63)
Obese (BMI >30)	18.6 (85)	3.7 (1)	25.7 (69)	9.3 (15)
Tobacco use				
Smoker	10.8 (49)	3.8 (1)	13.0 (35)	8.2 (13)
Former smoker	84.6 (384)	76.9 (20)	83.3 (224)	88.1 (140)
Never smoked	4.6 (21)	19.2 (5)	3.7 (10)	3.8 (6)
Education				
Low	51.9 (235)	34.6 (9)	54.9 (147)	49.7 (79)
Middle	34.6 (157)	50.0 (13)	33.2 (89)	34.6 (55)
High	13.5 (61)	15.4 (4)	11.9 (32)	15.7 (25)
Co morbidities (self-reported)	1.53 ±1.27	0.88 ±0.82	1.85 ±1.30	1.09 ±1.12
None	24.0 (109)	38.5 (10)	14.1 (38)	38.4 (61)
Fatigue	44.1 (200)	38.5 (10)	53.9 (145)	28.3 (45)
Back pain	24.4 (111)	7.7 (2)	30.0 (81)	17.6 (28)
Rheumatoid arthritis	20.9 (95)	11.5 (3)	26.4 (71)	13.2 (21)
Psychological problems	16.3 (74)	3.8 (1)	22.7 (61)	7.5 (12)
Diabetes mellitus	9.9 (45)	3.8 (1)	11.9 (32)	7.5 (12)
Cancer	1.3 (6)	-	1.9 (5)	0.6 (1)
Cardiac disease	15.9 (72)	11.5 (3)	17.1 (46)	14.5 (23)
Other	20.3 (92)	11.5 (3)	21.2 (57)	20.1 (32)

Data are expressed as % (N) or mean ± SD; FEV_1%: Forced expiratory volume in 1 second; FVC: Forced Vital Capacity; GOLD: global initiative for chronic obstructive lung disease; BMI: body mass index

'moderate COPD with mild impact on health status' or phenotype 3 'severe COPD with mild impact on health status' (33% and 46%, respectively), patients in the PR group primarily were identified as phenotype 2 'moderate COPD with high impact on health status' (59% vs 21% in the outpatient sample) and only 6% was identified as phenotype 1 'moderate COPD with mild impact on health status'.

Differences in change in health status between phenotypes in usual care (OP group) and in treatment response (PR group)

Of the 160 outpatients, 143 patients (89.4%) also participated one year later. Reasons for non-adherence were diverse, but no significant differences were found on the eleven outcome variables nor on the baseline characteristics between the responders and non-responders (data not shown). On a group level only significant change was found on fatigue between baseline and follow-up ($p < 0.01$, Table 5). Between phenotypes only very few significant differences were found over the one-year period in usual care. Phenotype 1 patients had significantly higher scores (more problems) in fatigue and health-related quality of life, and phenotype 3 patients had significant better FEV_1% predicted ($p < 0.01$, Table 5).

Significant improvements were found in 10 of 11 sub-domains in the total PR group when post-rehabilitation scores were compared to pre-rehabilitation scores (Table 6). Major differences were found between the three phenotypes in the number of significantly improved sub-domains at end of rehabilitation, varying from four (phenotype 1) to ten significantly improved sub-domains (phenotype 2) (Table 6). The different patterns of improvement between the three phenotypes for each sub-domain are presented in Figure 3.

DISCUSSION

In the present study we identified three clinical phenotypes based on a wide variety of parameters measuring aspects of physiological functioning, symptoms, functional impairment, and quality of life in a group of outpatients with stable COPD GOLD 2-3. The main differences between phenotypes were based on the relative balance between physiological disease severity on the one hand and the severity of symptoms, functional impairment, and quality of life on the other, which is assumed to be a reflection of the degree of adaptation to the disease. There was no change in almost any of the health status sub-domains in the usual care group over a one-year period, but there were significant improvements in almost all of the health status sub-domains in patients who were included in the pulmonary rehabilitation program.

Phenotype 1 ('moderate COPD – low impact') was characterized by moderate COPD and mild problems in the domains symptoms, functional impairment, and quality of life, which were in balance with disease severity. Clearly, this phenotype can be labelled as 'adapted'. Phenotype 2 ('moderate COPD - high impact') experienced severe problems in

Table 5 Change in health status after one year in outpatients; for total group and each phenotype

	All outpatients (N=143)			Phenotype 1 (n=51) moderate COPD – mild impact health status			Phenotype 2 (n=31) moderate COPD – high impact health status			Phenotype 3 (n=61) severe COPD – mild impact health status		
	baseline	12 months	p	baseline	12 months	p	baseline	12 months	p	baseline	12 months	p
Physiological Functioning												
FEV_1% of pred	52.0±13.8	53.5±14.0	0.06	60.8±11.5	61.2±11.1	0.77	53.3±12.8	53.3±12.5	0.99	44.7±11.7	47.6±13.9	**<0.01**
BMI	25.7±3.9	25.9± 4.1	0.19	24.9±3.1	25.0±3.3	0.35	27.1±4.4	27.6±4.8	0.05	25.7±4.1	25.7±4.1	0.96
Symptoms												
Subjective Symptoms	7.1±4.7	7.2±4.5	0.94	4.5±3.4	4.9±3.8	0.47	11.4±3.7	10.4±3.5	0.23	7.1±4.6	7.3±4.4	0.65
Dyspnea Emotions	9.7±3.3	10.0±3.3	0.29	9.4±3.2	9.1±3.1	0.62	11.8±3.7	11.7±3.8	0.87	9.0±2.7	9.9±2.9	0.02
Fatigue	26.8±11.0	29.7±11.4	**<0.01**	20.9±7.5	25.8±9.1	**<0.01**	39.6±8.9	40.3±9.6	0.75	25.0±9.1	27.5±10.8	0.04
Functional Impairment												
Subjective Impairment	9.9±5.0	10.3±4.9	0.16	7.0±2.9	8.0±3.3	0.02	15.8±5.0	14.5±4.4	0.09	9.2±3.8	10.3±4.8	0.13
Behavioral Impairment	15.2±13.1	15.2±14.7	0.96	8.0±8.0	7.9±8.4	0.91	30.2±12.4	29.4±16.6	0.80	13.3±10.6	13.9±12.8	0.59
Quality of Life												
General QoL	14.0±12.0	15.1±12.7	0.13	9.4±6.0	10.5±8.5	0.34	29.5±13.8	28.5±15.6	0.54	10.0±7.6	12.0±9.0	0.03
HrQoL	4.0±1.6	4.3±1.7	0.09	3.2±0.9	4.0±1.6	**<0.01**	6.0±1.6	5.5±1.3	0.07	3.7±1.3	3.9±1.8	0.39
Satisfaction Relations	3.1±1.4	2.9±1.5	0.18	2.8±1.1	2.8±1.6	0.80	4.4±1.9	3.7±1.6	0.02	2.7±0.9	2.7±1.3	0.93

Data are represented as mean ±SD, p-values in bold: significantly different between baseline and after 1 year (paired t-test, p< 0.01), data on exercise capacity was not collected after one year. FEV_1%: forced expiratory volume in 1 second; BMI: body mass index; VO_2max: maximal oxygen uptake; QoL: Quality of Life; HrQoL: Health Related Quality of Life

health status despite moderate disease severity. In these patients there is a clear imbalance between disease severity and impact on symptoms, functional impairment, and quality of life. Therefore this phenotype was labelled as 'non-adapted'. Phenotype 3 ('severe COPD – low impact') is more difficult to interpret. In fact, similar to phenotype 2, an imbalance was observed between disease severity on the one hand and severity of symptoms, functional impairment, and quality of life, but in reversed direction. Phenotype 3 patients showed much lower impact on symptoms, functional impairment, and quality of life than would be expected based on their severe COPD. Does this particular imbalance in phenotype 3 indicate extremely well adapted patients? Or does this imbalance indicate non-adapted patients. In clinical practice patients who report mild or no symptoms, functional impairment, and good quality of life despite severe COPD are well recognized. In some of these patients this may be a reflection of very adequate adaptation to the disease. But other patients with this profile tend to ignore and trivialize their symptoms, or simple are not sensitive to bodily symptoms, which eventually may lead to an escalation of problems in health status. These patients in clearly are not well adapted. This subgroup of patient may be labelled 'at risk'. Future research and clinical testing is needed to shed more light on this particular phenotype.

In searching for more homogeneous COPD subgroups, this is the first study that includes such a large set of parameters measuring symptoms, functional impairment, and quality of life, in addition to parameters measuring physiological functioning. In line with other studies performing cluster analysis [3, 4] we confirmed that airflow limitation was not the only characteristic in the identified clinical phenotypes. Burgel et al [4] found marked differences between phenotypes in reported symptoms and quality of life regardless of COPD severity. We observed the same phenomenon in the present study, but also incorporated functional impairment as a domain and examined the role of adaptation in the identified clusters. The discriminant analysis revealed that all four main domains of health status are relevant in this respect, as shown by the fact that of each main domain one or two sub-domains were necessary to assign new patients to one of the identified clinical phenotypes.

Studies to date using cluster analysis recommend to evaluate treatment response [3, 5, 20-23]. Although such studies have been performed evaluating the effect of pharmacological treatment in diverse phenotypes [24, 25], similar studies with respect to non-pharmacological treatments are lacking. In the usual care group over one year only significant changes were found in fatigue. The pulmonary rehabilitation program, with its strong emphasis on teaching the patient self-management strategies in order to improve adaptation to the disease did show major improvements in health status. Especially in the non-adapted phenotype 2 the improvements in experienced symptoms, impairment and quality of life were most pronounced.

With respect to the change in health status over a one-year period in the usual care sample (OP group), on a group level significant changes were found only in fatigue.

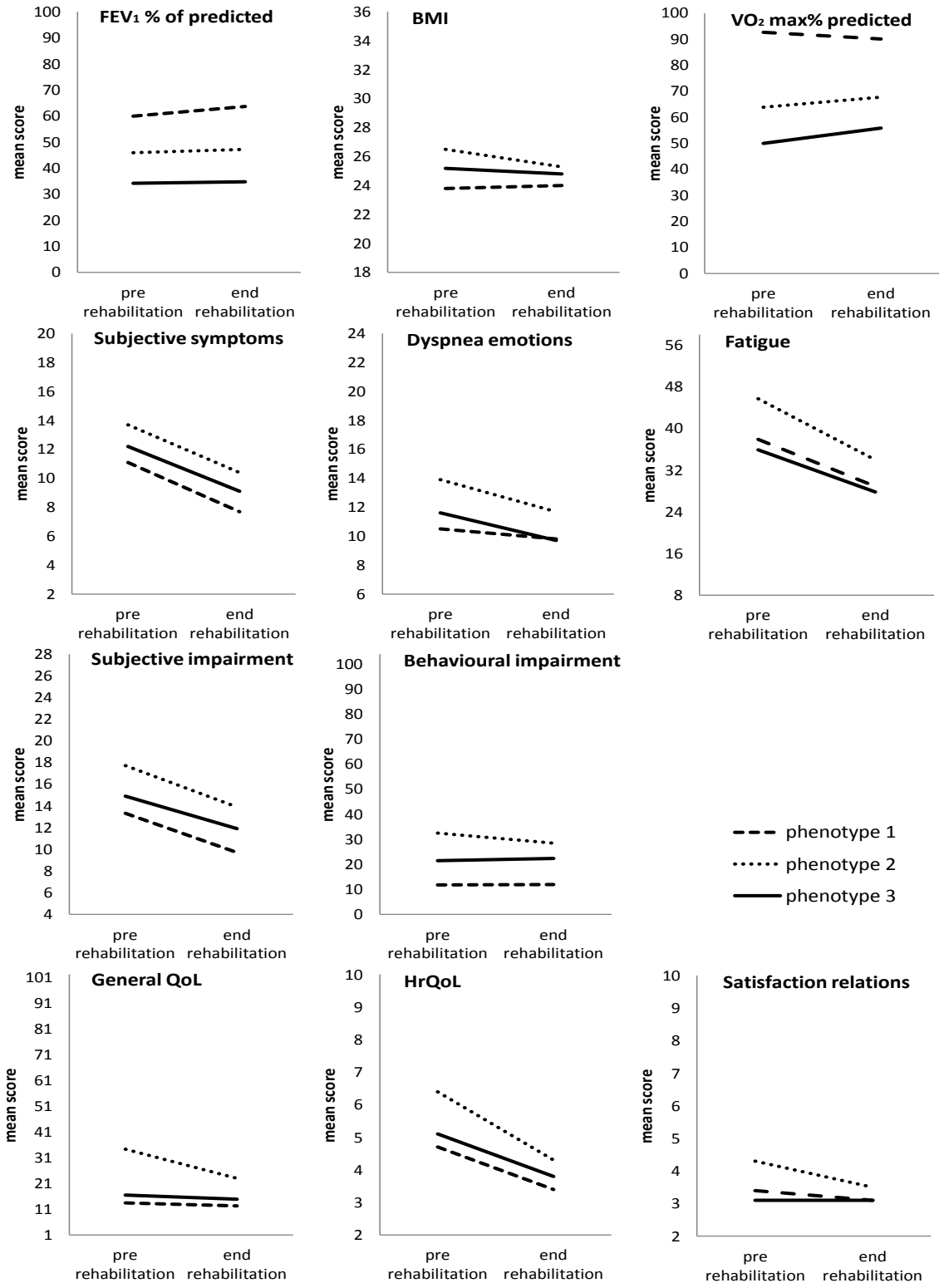


Figure 3 Mean scores on each sub-domain at start and end of pulmonary rehabilitation for each phenotype Note: the vertical axis displays the minimal and maximal score for that specific sub-domain. Higher scores mean more impact on the sub-domain, except for FEV_1% of predicted and VO_2 max% predicted where 100% represent the ideal score.

In contrast, in the PR group statistically significant and clinically relevant improvements were found in all sub-domains except for airflow limitation. Moreover, the three clinical phenotypes showed a different pattern of change in the sub-domains of health status with respect to response to treatment.

Limitations

In the present study we included a group of patients with stable GOLD moderate to severe COPD (II-III) and we excluded co-morbidities dominating health status to identify clinical phenotypes. This selection of patients may limit generalizability of the results. Ideally, the cluster analysis should be replicated in a group of COPD patients with the complete spectrum of GOLD I-IV to examine whether all possible clinical phenotypes based on health status were identified.

We included a limited set of systemic effects of COPD (FEV_1, BMI, RV and TLC). Theoretically, other systemic effects such as muscle strength may/could be responsible for the observed discrepancies. Future studies should examine the role of systemic effects of COPD in these clusters, especially in phenotype 2.

Although, low numbers of non-adapted patients (phenotype 2) were found in the OP group, we found similar profiles in the PR group with respect to the balance/imbalance between the domains in phenotype 2. Due to the low number of patients in phenotype 1 'moderate COPD-mild impact on health status', in the PR group, the effect of rehabilitation in phenotype 1 patients should be interpreted with caution.

In this study the timeframes to examine the effect of usual care and the inpatient pulmonary rehabilitation on health status were different. This could lead in favour of the effects of pulmonary rehabilitation on health status. Ideally, data from one year after completion of the inpatient pulmonary rehabilitation program would be compared to the data before the pulmonary rehabilitation to examine whether the PR effects remain stable over a one-year follow-up, and in particular if patients remain more adapted than compared to start of rehabilitation.

Implications

The findings of the present study and other studies that performed cluster analysis have important implications for future studies and clinical practice. These studies have shown that COPD patients represent a very heterogeneous group of persons. Using cluster analyses it is possible to identify more homogeneous sub-groups that respond differently to pharmacological and non-pharmacological treatment. The present study showed that, besides phenotypes based on different pathophysiological mechanisms, also phenotypes exists that are more determined by behavioral aspects (i.e. adapting to the disease by self-management behaviours).

Knowing which type of patients will benefit from specific interventions, will help in guiding patient tailored treatment and improve outcome and cost-effectiveness of both pharmacological and non-pharmacological treatment. Eventually, this could lead to different sets of custom made interventions that are effective for a specific phenotype.

Table 6 Change in health status after an inpatient pulmonary rehabilitation; for total group and each phenotype

	All patients (N=459)			Phenotype 1 (n=27) moderate COPD – mild impact health status			Phenotype 2 (n=271) moderate COPD – high impact health status			Phenotype 3 (n=161) severe COPD – mild impact health status		
	before	end	p	before	end	p	before	end	p	before	end	p
Physiological functioning												
FEV_1% of pred	42.8±17.9	43.9±20.6	0.03	60.0±18.3	63.7±20.1	0.22	46.0±18.3	47.2±21.3	0.10	34.2±12.1	34.8±14.6	0.37
BMI	25.9±5.4	25.1±6.6	**<0.01**	23.8±3.8	24.0±3.5	0.28	26.5±6.0	25.3±7.4	**<0.01**	25.2±4.3	24.8±5.6	0.29
VO_2% of pred^	60.8±19.0	64.9±19.3	**<0.01**	92.7±12.0	90.1±17.8	0.53	63.9±16.0	67.7±17.7	**0.01**	50.0±14.0	55.8±15.5	**<0.01**
Symptoms												
Subjective Symptoms	13.0±3.8	9.8±4.3	**<0.01**	11.1±3.9	7.7±3.5	**0.01**	13.7±3.6	10.4±4.2	**<0.01**	12.2±4.0	9.1±4.4	**<0.01**
Dyspnea Emotions	12.9±4.1	10.9±4.0	**<0.01**	10.5±2.9	9.8±3.9	0.29	13.9±3.9	11.7±4.1	**<0.01**	11.6±4.2	9.7±3.6	**<0.01**
Fatigue	41.8±9.4	31.5±10.6	**<0.01**	37.9±9.7	28.9±9.2	**<0.01**	45.7±7.3	34.0±9.9	**<0.01**	35.9±9.3	27.8±10.7	**<0.01**
Functional Impairment												
Subjective Impairment	16.5±5.2	13.0±5.2	**<0.01**	13.3±5.6	9.7±4.1	**<0.01**	17.7±4.9	13.9±5.0	**<0.01**	14.9±5.2	11.9±5.1	**<0.01**
Behavioral Impairment	27.4±14.2	23.5±14.5	**<0.01**	11.8±6.4	11.9±9.4	0.95	32.4±14.3	28.4±14.6	**<0.01**	21.4±10.5	22.4±13.2	0.35
Quality of Life												
General QoL	26.8±14.8	19.5±12.5	**<0.01**	13.4±7.1	12.3±11.5	0.64	34.3±13.6	22.9±13.0	**<0.01**	16.5±8.6	14.9±9.6	0.05
HrQoL	5.8±1.7	4.1±1.7	**<0.01**	4.7±1.5	3.4±1.8	**0.01**	6.4±1.5	4.3±1.7	**<0.01**	5.1±1.5	3.8±1.6	**<0.01**
Satisfaction Relations	3.9±1.8	3.3±1.7	**<0.01**	3.4±1.9	3.1±1.7	0.56	4.3±1.9	3.5±1.7	**<0.01**	3.1±1.5	3.1±1.6	0.82

Data are represented as mean ±SD, p-values in bold: significantly different before and end rehabilitation (paired t-test, p< 0.01, ^ 151 patients performed a maximal cycle ergometry test at the end of the rehabilitation (respectively, 13/77/61 patients per phenotype), the other patients performed an endurance cycle ergometry (data not shown); FEV_1%: forced expiratory volume in 1 second; BMI: body mass index; VO_2max: maximal oxygen uptake; QoL: Quality of Life; HrQoL: Health Related Quality of Life

Usual care generally has a focus on physiological assessment and pharmacological treatment. The fact that in the usual care group (OP group) 20% of patients was classified as non-adapters calls for the need of regular screening for the degree of adaptation to the disease as part of usual care. In addition, in the usual care group non-adapted patients did not show any improvement in health status, whereas non-adapted patients showed major improvements in health status in the pulmonary rehabilitation group. Clearly, non-adapted patients profit from interventions aimed at improving self-management behaviour, which is one of the key components of the pulmonary rehabilitation program as stated by the American Thoracic Society and European Respiratory Society (ATS/ERS) [17]. In adapted patients probably a limited selection of treatment modalities may be sufficient. Future studies are necessary to identify the minimal treatment components for each clinical phenotype to optimize physiological functioning and adaptation to the disease in a patient.

Phenotype 3 'severe COPD and mild impaired health status' patients, are a group of patients that need special attention. Although some of these patients may be well adapted to the disease, others may be at risk for poor adaptation by ignoring symptoms and impairments. Moreover, these patients have severe COPD. Regular check-ups of these patients are warranted.

Conclusions

Studies to date identified phenotypes that are mainly based on different underlying pathophysiological mechanisms. In the present study we have identified phenotypes that are based more on behavioral aspects. Whereas, pathophysiological phenotypes may help guiding pharmacological treatment, the phenotypes identified in the present study may help to improve (cost-)effectiveness of non-pharmacological treatments, such as self-management programs and pulmonary rehabilitation programs.

REFERENCES

1. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. 2014: Available from: http://www.goldcopd.org/
2. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, Tal-Singer R, Wouters E, Yates JC, Vestbo J. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respiratory Research 2010: 11:122.
3. Beasley R, Weatherall M, Travers J, Shirtcliffe P. Time to define the disorders of the syndrome of COPD. Lancet. 2009: 374(9691):670-672.
4. Burgel PR, Paillasseur JL, Caillaud D, Tillie-Leblond I, Chanez P, Escamilla R, Court-Fortune I, Perez T, Carre P, Roche N, Initiatives BSC. Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. European Respiratory Journal 2010: 36(3):531-539.
5. Fingleton J, Weatherall M, Beasley R. Towards individualised treatment in COPD. Thorax. 2011: 66(5):363-364.

6. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. American Journal of Respiratory and Critical Care Medicine. 2011: 184(6):662-671.
7. Cho MH, Washko GR, Hoffmann TJ, Criner GJ, Hoffman EA, Martinez FJ, Laird N, Reilly JJ, Silverman EK. Cluster analysis in severe emphysema subjects using phenotype and genotype data: an exploratory investigation. Respiratory Research. 2010: 11:30.
8. Garcia-Aymerich J, Gomez FP, Benet M, Farrero E, Basagana X, Gayete A, Pare C, Freixa X, Ferrer J, Ferrer A, Roca J, Galdiz JB, Sauleda J, Monso E, Gea J, Barbera JA, Agusti A, Anto JM, Group P-CS. Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. Thorax. 2011: 66(5):430-437.
9. Wardlaw AJ, Silverman M, Siva R, Pavord ID, Green R. Multi-dimensional phenotyping: towards a new taxonomy for airway disease. Clinical and Experimental Allergy. 2005: 35(10):1254-1262.
10. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, Aldington S, Beasley R. Distinct clinical phenotypes of airways disease defined by cluster analysis. European Respiratory Journal. 2009: 34(4):812-818.
11. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Journal of the American Medical Association. 1995: 273(1):59-65.
12. Vercoulen, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavavioral Medicine. 2008: 15(4):263-279.
13. Verhage TL, Vercoulen JH, van Helvoort HA, Peters JB, Molema J, Dekhuijzen PN, Heijdra YF. Maximal exercise capacity in chronic obstructive pulmonary disease: a limited indicator of the health status. Respiration; international review of thoracic diseases. 2010: 80(6):453-462.
14. Effing TW, Bourbeau J, Vercoulen J, Apter AJ, Coultas D, Meek P, Valk P, Partridge MR, Palen J. Self-management programmes for COPD: moving forward. Chronic Respiratory Disease. 2012: 9(1):27-35.
15. Vercoulen. A simple method to enable patient-tailored treatment and to motivate the patient to change behavior. Chronic Respiratory Disease. 2012: In press.
16. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. Proceedings of the American Thoracic Society. 2012: 9(1):9-18.
17. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Molken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF, Rehabilitation AETFoP. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013: 188(8):e13-64.
18. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in

routine care: the Nijmegen Clinical Screening Instrument. Quality of Life Research. 2009: 18(7): 901-912.
19. Ward JH. Hierarchical grouping to optimize an objective function. Journal of the American Statistical Association. 1963: 58(301):236-244.
20. Vercoulen, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
21. Maille AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA. The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QOL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91(5):297-309.
22. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical Care. 1981: 19(8):787-805.
23. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour and Research Therapy. 1997: 35(8):785-791.
24. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. Journal of Personality Assessment. 1985: 49(1):71-75.
25. Agusti A, Sobradillo P, Celli B. Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. American Journal of Respiratory and Critical Care Medicine. 2011: 183(9):1129-1137.
26. Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. Lancet. 2011: 378(9795):1038-1047.
27. Shirtcliffe P, Weatherall M, Travers J, Beasley R. The multiple dimensions of airways disease: targeting treatment to clinical phenotypes. Current Opinion of Pulmonary Medicine. 2011: 17(2):72-78.
28. Weatherall M, Shirtcliffe P, Travers J, Beasley R. Use of cluster analysis to define COPD phenotypes. European Respiratory Journal. 2010: 36(3):472-474.
29. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. American Journal of Respiratory and Critical Care Medicine. 2012: 186(1):48-55.
30. Miravitlles M, Soler-Cataluna JJ, Calle M, Molina J, Almagro P, Quintano JA, Riesco JA, Trigueros JA, Pinera P, Simon A, Lopez-Campos JL, Soriano JB, Ancochea J, Spanish Society of P, Thoracic S. Spanish COPD Guidelines (GesEPOC): pharmacological treatment of stable COPD. Spanish Society of Pulmonology and Thoracic Surgery. Archives of Bronconeumology. 2012: 48(7):247-257.

CHAPTER 6

Health status measurement in patients with severe asthma

Jeannette B Peters
Lucia H Rijssenbeek- Nouwens
Aad O Bron
Karin B Fieten
Els J M Weersink
Elisabeth H Bel
Jan H Vercoulen

Respiratory Medicine. 2014: 108:278-286

ABSTRACT

Background

Patients with severe asthma experience problems in different areas of their health status. Identification of these areas will provide insight in the patients needs and perhaps what determines the burden of disease. The Nijmegen Clinical Screening Instrument (NCSI) was recently developed for use in clinical practice in patients with COPD and provides a detailed picture of the patients' physiological functioning, symptoms, functional impairment, and Quality of Life. Main purpose of this study is to evaluate the use of the NCSI to measure health status as compared to the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) in patients with severe asthma.

Methods

The NCSI, AQLQ, and ACQ were measured in 167 patients with severe asthma. Pearson correlations were calculated between NCSI sub-domains and the AQLQ domains and the ACQ.

Results

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

Conclusions

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

INTRODUCTION

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

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

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

Although developed and validated in patients with COPD [11], have previous studies shown that all NCSI sub-domains are relevant in other diseases as well, including Q-fever[12, 13], and cardiac diseases (submitted). We hypothesized that the NCSI can be used also in patients with asthma. Astma and COPD have overlapping clinical characteristics and both patient groups report similar problems in health status. Moreover, patients with severe asthma are known to experience severe symptoms, functional impairment, and lower QoL [1-6]. Therefore, a group of patients with severe asthma would be most suitable to examine whether the NCSI can identify problems in health status in patients with severe asthma.

The main purpose of this study is to evaluate the NCSI in measuring the unmet needs in patients with severe asthma. The primary aim is to evaluate the internal consistency of the NCSI, and to investigate the relationships between the sub-domains of the NCSI, the ACQ

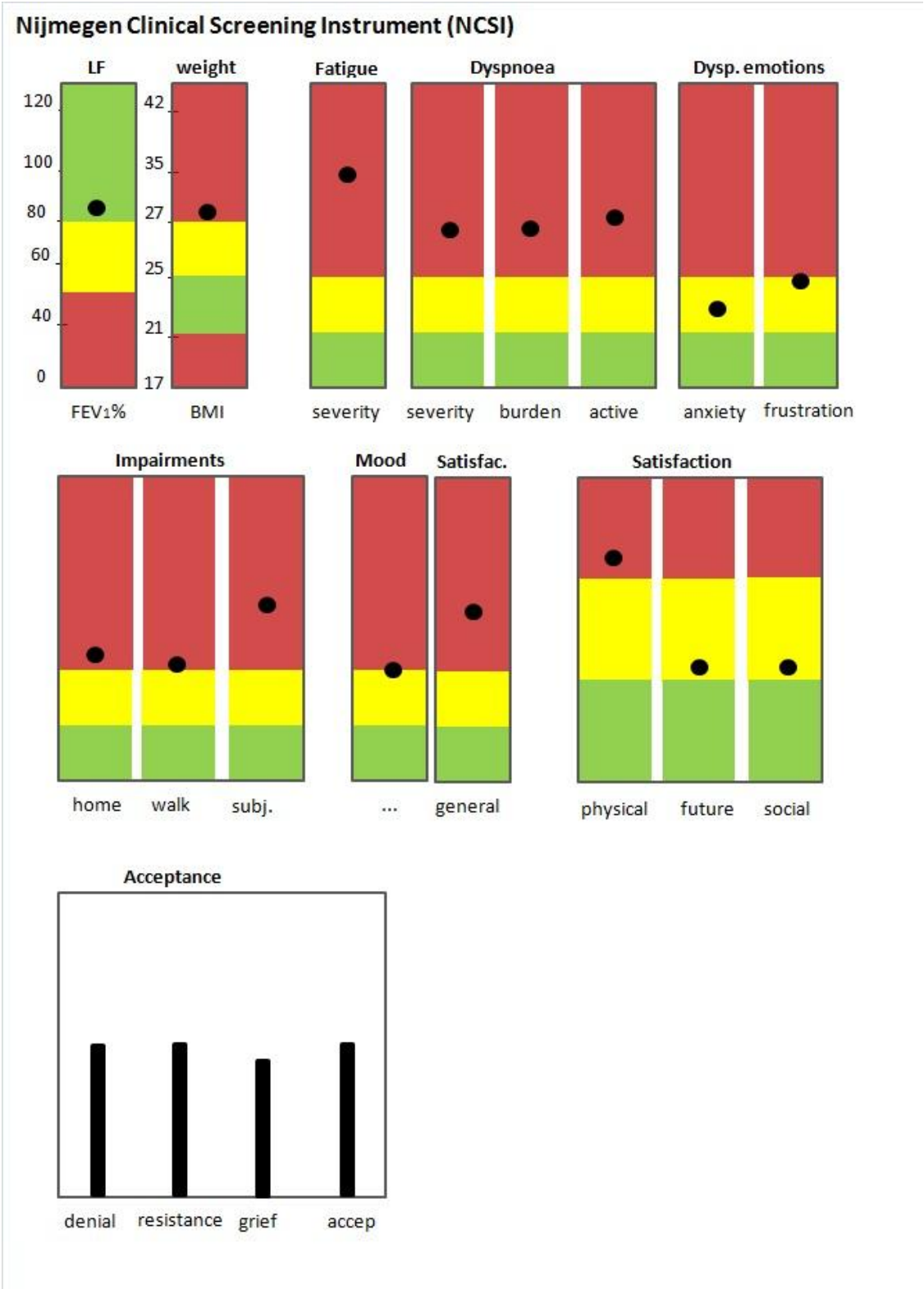


Figure 1 The PatientProfileChart a graphical representation of the patient's scores on the diverse aspects of health status as measured by the NCSI. Note: in this figure we plotted the mean score of the study group (blue dots) on that particular aspect instead of the individual score which is normally plotted in the graphs. The green area represents normal functioning, yellow area mild problems, and red area severe problems

total, and the AQLQ domains in patients with severe asthma. The secondary aim is to evaluate to what extent the NCSI measures other sub-domains of health status as compared to the disease specific AQLQ and ACQ, and whether these sub-domains are relevant in patients with severe asthma.

MATERIALS AND METHODS

Study design

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

Study population

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

Questionnaires

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

ACQ. The Asthma Control Questionnaire (ACQ) [7, 16] consists of six items which are scored from 0 (totally controlled) to 6 (severely uncontrolled) covering day and nighttime symptoms, activity limitations and rescue bronchodilator use.

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

Domain/ sub-domain	Definition	Instruments/measurement	Number of items
Physiological functioning			
Airflow		Post bronchodilator FEV_1% predicted	
Body Composition		Body Mass Index	
Symptoms			
Subjective Symptoms	The patient's overall burden of pulmonary symptoms	PARS-D Global Dyspnea Activity [20] PARS-D Global Dyspnea Burden [20]	2
Dyspnea Emotions	The level of frustration and anxiety a person experiences when dyspnoeic	DEQ Frustration [20] DEQ Anxiety [20]	6
Fatigue	The level of experienced fatigue	CIS Subjective fatigue [21]	8
Functional Impairment			
Behavioral Impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP Home Management [22] SIP Ambulation [22]	22
Subjective Impairment	The experienced degree of impairment in general	QoLRiQ General Activities [10]	4
Quality of life			
General Quality of Life	Mood and the satisfaction of a person with his/her life as a whole	BDI Primary Care [17] Satisfaction With Life Scale [19]	12
Health-related Quality of Life	Satisfaction related to physical functioning and the future	Satisfaction physiological functioning [20] Satisfaction future [20]	2
Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction spouse [20] Satisfaction social [20]	2

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

The cut-off point for well controlled asthma is lower than 1.5 [7].

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

Measures

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

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

Statistics

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

RESULTS

Subject characteristics

One hundred and eighty patients were admitted to the high altitude clinic between January 2008 and January 2010, of which 167 agreed to participate in the study. Thirteen patients

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

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

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

were not able to fill the questionnaires adequately because of illiteracy or did not agree to participate for personal reasons. The baseline characteristics of the 167 patients with severe asthma included in this study are presented in Table 2. Uncontrolled asthma was found in 91% (ACQ >1.5) of the patients in this study.

NCSI-scores in severe asthma patients

Overall, high percentages of severe problems were found in the sub-domains of symptoms, functional impairment, and QoL (Fig 2.). The most prevalent sub-domains with severe impairment were subjective symptoms (82.0%), fatigue (90.4%), subjective impairment (86.8%), and general QoL (81.4%). Furthermore, 31.7% of the patients had clinically relevant

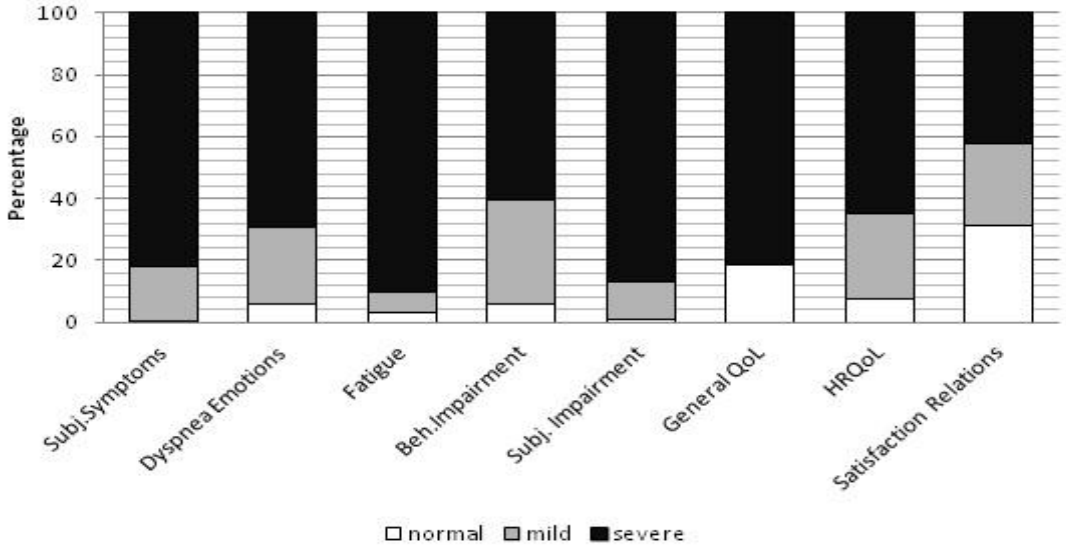


Figure 2 Percentages of patients with asthma with normal functioning, mild problems and severe problems for each sub-domain of the NCSI

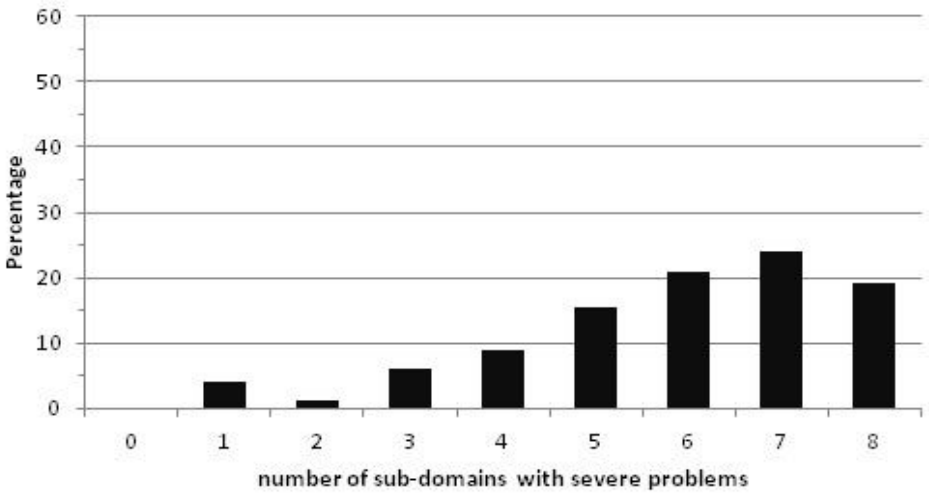


Figure 3 Distribution of percentages of patients with severe asthma with severe problems on *n* number of sub-domains of the NCSI

depressive symptoms (subscale within sub-domain general QoL, not shown).

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

Inter correlations of the questionnaires

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

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

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

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

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

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

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

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

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

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

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

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

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

Note. Pearson correlations between the sub-domains NCSI, ACQ, AQLQ for patients with difficult to control asthma at start of rehabilitation. N = 167 except for behavioral impairment due to technical error (N = 53). Correlations > 0.70 in **bold**. Correlations in '***bold-italic***' nearly reach conceptual similarity.ns = not significant.

Reliability of the questionnaires

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

Conceptual similarity between the questionnaires

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

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

Nor the ACQ or domains of the AQLQ did show conceptual similarity with the NCSI sub-domains fatigue, behavioral impairment, general QoL, health-related Qol, and

satisfaction with relations. The NCSI, ACQ, and AQOLQ were not significantly related to FEV_1, Fe_{NO}, BMI.

DISCUSSION

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

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

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

The present study shows that all NCSI subscales represent highly relevant sub-domains of health status in patients with severe asthma. In addition, heterogeneity was found between patients with respect to the number of sub-domains and in the combination

of sub-domains on which patients experienced severe problems. Low to absent correlations were not only found between the non-physiological sub-domains of the NCSI, but also between physiological functioning and symptoms, behavioral impairment, and QoL. This is not a new phenomena, Haldar etal [29] also found that symptom perception is not always in concordance with eosinophilic airway inflammation, and concluded that both, symptoms and physiologic parameters, have to be measured to get a complete picture.

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

The reason for this study was the need for an instrument that would enable a detailed evaluation of the needs of patients with severe asthma and that could help to identify the factors that aggravate, complicate, or influence disease perception. The NCSI provides a detailed assessment of health status, and includes normative data, which render the patient's scores on each sub-domain clinically meaningful [11]. The powerful mechanism is not the NCSI as instrument per sé, but by discussing the PatientProfileChart with the patient. The PatientProfileChart visualizes on which sub-domain a patient functions normally and on which sub-domain a patient experience severe problems. The PatientProfileChart allows the doctor and other healthcare providers to quickly identify the factors leading to disease burden by discussing the results [30]. Moreover, the discussion with the patient also facilitates shared-decision making, which has proven to be important in promoting adherence [31]. Moreover, the complexity of the balance between health status and the underlying problems and self-management capacities, may become visible in the discussion. This information may help in guiding non-pharmacological treatment since pharmacological treatment alone seems to be insufficient in patients with severe asthma [31]. In COPD this approach have been implemented in usual care since several years and has proven its clinical relevance. The next step would be to implement the NCSI in treatment of patients with severe asthma, and examine its sensitivity to change.

CONCLUSIONS

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

Conflicts of interest: The authors JP, LR, KF, AB, EW and JV declare no conflict of interest. EHB received in behalf of the department of Respiratory Medicine of the Academic Medical Centre grants from the Dutch Asthma Foundation and from Novartis, GSK, and Chiesi. She received speaker fees from GSK, and consultant fees from Novartis and GSK, which were donated to the department.

REFERENCES

1. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992: 47(2):76-83.
2. Haselkorn T, Chen H, Miller DP, Fish JE, Peters SP, Weiss ST, et al. Asthma control and activity limitations: insights from the Real-world Evaluation of Asthma Control and Treatment (REACT) study. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, & Immunology. 2010: 104(6):471-7.
3. Centanni S, Di Marco F, Castagna F, Boveri B, Casanova F, Piazzini A. Psychological issues in the treatment of asthmatic patients. Respiratory Medicine. 2000: 94(8):742-9.
4. Katz PP, Morris A, Julian L, Omachi T, Yelin EH, Eisner MD, et al. Onset of depressive symptoms among adults with asthma: results from a longitudinal observational cohort. Primary Care Respiratory Journal. 2010: 19(3):223-30.
5. Lavoie KL, Bacon SL, Barone S, Cartier A, Ditto B, Labrecque M. What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? Chest 2006: 130(4):1039-47.
6. Lavoie KL, Bouthillier D, Bacon SL, Lemiere C, Martin J, Hamid Q, et al. Psychologic distress and maladaptive coping styles in patients with severe vs moderate asthma. Chest. 2010: 137(6):1324-31.
7. Juniper EF, Bousquet J, Abetz L, Bateman ED, Committee G. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respiratory Medicine. 2006: 100(4):616-21.
8. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999: 115(5):1265-70.
9. Jones PW, Quirk FH, Baveystock CM. The St George Respiratory Questionnaire. Respiratory Medicine 1991: 85:25-31.
10. Maille AR, Koning CJ, Zwinderman AH, Willems LN, Dijkman JH, Kaptein AA. The development of the 'Quality-of-life for Respiratory Illness Questionnaire (QOL-RIQ)': a disease-specific quality-of-life questionnaire for patients with mild to moderate chronic non-specific lung disease. Respiratory Medicine. 1997: 91(5):297-309.

11. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. Quality of Life Research. 2009: 18(7):901-12.
12. Limonard GJ, Peters JB, Nabuurs-Franssen MH, Weers-Pothoff G, Besselink R, Groot CA, et al. Detailed analysis of health status of Q fever patients 1 year after the first Dutch outbreak: a case-control study. QJM: An International Journal of Medicine. 2010: 103(12):953-8.
13. Morroy G, Peters JB, van Nieuwenhof M, Bor HH, Hautvast JL, van der Hoek W, et al. The health status of Q-fever patients after long-term follow-up. BMC Infectious Disease. 2011: 11:97.
14. Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, Wagener AH, Wagers SS, Sterk PJ, Compton CH. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax. 2011: 66(10):910-7.
15. National Institutes of Health. National Heart, Lung, and Blood Institute. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/ WHO Workshop Report. 2008. http://www.ginasthma.org/.
16. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. European Respiratory Journal. 1999;14(4):902-7.
17. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. Behaviour Research and Therapy. 1997: 35(8):785-791.
18. Bergner M. Development, testing, and use of Sickness Impact Profile. In: Walker RS, Rosser RM, editors. Quality of life assessment: Key issues in the 1990s: Kluwer Academic Publishers, 1993:95-111.
19. Diener E, Emmons RA, Larsen RJ, Griffin S. The satisfaction with life scale. Journal of Personality Assessment. 1985: 49(1):71-75.
20. Vercoulen JH, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering Hl. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavioral Medicine. 2008: 15(4):263-279.
21. Vercoulen JH, Swanink CMA, Galama JMD, Fennis JFM, van der Meer JWM, Bleijenberg G. Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
22. Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Medical Care. 1981: 19(8):787-805.
23. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. American Journal of Respiratory and Critical Care Medicine. 2005: 171(8):912-930.
24. Rijssenbeek-Nouwens LH, Fieten KB, Bron AO, Hashimoto S, Bel EH, Weersink EJ. High-altitude treatment in atopic and nonatopic patients with severe asthma. European Respiratory Journal. 2012: 40(6):1374-1380.
25. Busse WW, Wenzel SE, Meltzer EO, Kerwin EM, Liu MC, Zhang N, et al. Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients. Journal of Allergy and Clinical Immunology. 2013: 131(2):339-345.

26. Mancuso CA, Choi TN, Westermann H, Wenderoth S, Wells MT, Charlson ME. Improvement in asthma quality of life in patients enrolled in a prospective study to increase lifestyle physical activity. Jornal of Asthma. 2013: 50(1):103-107.
27. Turner S, Eastwood P, Cook A, Jenkins S. Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. Respiration. 2011: 81(4):302-310.
28. Chhabra SK, Chhabra P. Gender differences in perception of dyspnea, assessment of control, and quality of life in asthma. Journal of Asthma. 2011: 48(6):609-615.
29. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. American Journal of Respiratory and Critical Care Medicine. 2008: 178(3):218-224.
30. Vercoulen JH. A simple method to enable patient-tailored treatment and to motivate the patient to change behaviour. Chronic Respiratory Disease. 2012: 9(4):259-268.
31. Bourdin A, Halimi L, Vachier I, Paganin F, Lamouroux A, Gouitaa M, et al. Adherence in severe asthma. Clinical and experimental allergy: journal of the British Society for Allergy and Clinical Immunology. 2012: 42(11):1566-1574.

CHAPTER 7

Detailed analysis of health status of Q fever patients 1 year after the First Dutch outbreak: a case-control study

Gijs J M Limonard
Jeannette B Peters
Marrigje H Nabuurs-Franssen
Ineke Weers-Pothoff
Rob Besselink
Cees A R Groot
P N Richard Dekhuijzen
Jan H Vercoulen

QJM- an International Journal of Medicine. 2010: 103(12):953-958

ABSTRACT

Background

Q fever is a zoonosis caused by the obligate intracellular bacterium *Coxiella burnetii*. The two long term complications, after primary infection, are chronic Q fever in ~1% of patients, and a chronic fatigue syndrome in 10-20%. However, the existence of a protracted decreased health status after Q fever remains controversial.

Aim

To determine the health status of the patients of the Q fever outbreak in The Netherlands in 2007, 1 year after primary infection.

Design

Cross-sectional case-control study.

Methods

Health status of the patients from the 2007 Dutch Q fever outbreak was compared to age-, sex- and geographically matched and Q fever seronegative controls. Health status of both patients and controls was assessed with the Nijmegen Clinical Screening Instrument (NCSI).

Results

Fifty-four Q fever patients provided 34 years of age- and sex-matched controls from the same neighbourhood. Eleven controls had positive Q fever serology and were excluded. Q fever patients had significantly more problems on the sub-domains of symptoms and functional impairment. Overall quality of life was decreased in both patients and controls, 59% vs. 39%, respectively, ns. Severe fatigue levels were present in 52% of patients vs. 26% in controls ($p< 0.05$).

Conclusion

These data support a sustained decrease in many aspects of health status in Q fever patients in The Netherlands, 1 year after primary infection.

INTRODUCTION

Q fever is a zoonosis caused by the obligate intracellular bacterium *Coxiella burnetii* [1]. In its acute form, Q fever generally presents as a mild flu-like syndrome, atypical pneumonia or hepatitis [1, 2]. After primary infection, ~1% of patients develop chronic Q fever, mainly as endocarditis in patients with pre-existing cardiac valvulopathies [1, 3].

In recent years, research groups have drawn attention to another, less known, chronic sequel to primary Q fever, which takes the form of a debilitating chronic fatigue syndrome lasting >6 months in up to circa 20% of patients [4-9]. However, despite these reports on post Q fever fatigue, the existence of a 'post Q fever fatigue syndrome' or QFS as a distinct clinicopathological entity remains controversial, especially in France and the US [1, 10].

In 2007, a goat farming-related Q fever outbreak of 73 cases was identified in the rural town of Herpen, The Netherlands [11]. Since then, an ongoing Q fever endemic has produced the Dutch province of North-Brabant as the currently most hyperendemic region in the world with more than 3000 acute Q fever cases in 2008 and 2009 [12, 13].

No data exist on the impact on the long-term impact on health status after acute Q fever in The Netherlands. The aim of the present study was to determine the health status of the patients of the Q fever outbreak in The Netherlands in 2007, 1 year after primary Q fever infection.

METHODS

Patients

All patients from the Q fever outbreak cluster in Herpen (n=73) were asked to participate. A case of acute Q fever was defined as any inhabitant of the outbreak cluster area who presented with compatible clinical symptoms and a positive serology defined by immunofluorescence assay (IFA) (Focus diagnostics). Positive serology was defined as both anti-phase II IgM and anti-phase II IgG antibodies with a 1:64 or greater dilution or a seroconversion consisting of a 4-fold increase of anti-Phase II IgG titer during follow-up. All Q fever patients were followed up serologically for a period of 1 year for antibodies against both Phase I and Phase II antigens, to exclude progression to chronic infection. As controls, Q fever patients were asked to bring along an age- and sex matched control subject from their neighbourhood, without a history of Q fever. Control subjects had to be age (±10 years) and sex matched to the patient. Control subjects were serologically tested for C. burnetii antibodies using IFA. Positive serological findings of Q fever excluded controls from the primary analysis. Documentation on actual significant comorbidity was available for all participants. All patients provided written informed consent. The study was approved by the local Ethical Board for Human Research. (Commissie Mensgebonden Onderzoek file-nr.: 2008/192, ABR nr.: NL24404.091.08).

Study design

The health status of the patients from the 2007 Q fever outbreak was compared to age-, sex- and geographically matched controls. Health status of both patients and controls was assessed with the Nijmegen Clinical Screening Instrument (NCSI) 1 year after the initial Q fever infection.

The Nijmegen Clinical Screening Instrument (NCSI)

In the literature, health status is defined as covering physiological functioning, symptoms, functional impairment in daily life, and quality of life (QoL) as main domains [14, 15]. These domains were shown empirically to be subdivided into many independent sub-domains [16]. The NCSI is an empirically composed battery of well validated instruments, that enable a detailed measurement of these sub-domains of health status [17]. See Table 1 for the tests and instruments by which the sub-domains of health status were measured. In the present study, the NCSI covers eight sub-domains of the main domains 'symptoms', 'functional impairment' and 'quality of life'. The clinical meaning of these main domains is given hereafter.

Table 1 Main domains and sub-domains of the NCSI, their corresponding instruments and subscales

Main domain	Sub-domain	Instrument subscale
Symptoms	Subjective symptoms	PARS-D Global dyspnea activity
		PARS-D Global dyspnea burden
	Dyspnea emotions	DEQ-frustration
		DEQ-anxiety
	Fatigue	Checklist Individual Strength
Functional impairment	Behavioral impairment	SIP home management
		SIP ambulation
	Subjective impairment	QOL-RIQ general activities
Quality of Life	General QoL	BDI primary care
		SWLS-total
	HRQoL	Satisfaction physical
		Satisfaction future
	Satisfaction relations	Satisfaction spouse
		Satisfaction social

Main domain subjective symptoms

The sub-domain subjective symptoms represent the patient's overall burden of dyspnea and experienced dyspnea during activities. The sub-domain dyspnea emotions embodies the level of frustration and anxiety a person experiences when dyspnoeic.

Main domain functional impairment

The sub-domain behavioral impairment represents the extent to which a person cannot perform specific and concrete activities, with respect to ambulation and activities at home,

as a result of having the disease. The sub-domain subjective impairment represents the experienced degree of impairment.

Main domain QoL

The sub-domain general QoL covers mood and satisfaction with life as a whole. The sub-domain HRQoL represents satisfaction with physical functioning and confidence in the future. The sub-domain satisfaction relations represents the satisfaction with (or absence of) the relationships with spouse and others.

The NCSI provides normative data for each sub-domain; increasing scores indicating normal functioning, mild problems or severe problems.

Statistical analysis

All quantitative data are presented as mean ± SD if normally distributed, otherwise median values (with range) are reported. Testing for differences between patients and controls was performed by Pearson's χ^2 or Mann-Whitney test when appropriate. Statistical significance is set at a $P< 0.05$. Data were analyzed with SPSS 14.

RESULTS

A total of 54 of the 73 (74%) Q fever patients from the 2007 Herpen outbreak agreed to participate. Thirty-four of these patients provided an age- and sex-matched control from the same neighbourhood. Eleven of these controls had positive Q fever serology and were excluded, leaving 23 seronegative controls for comparison. Characteristics of the study and seronegative control subjects are given in Table 2. Patients and controls proved to be well matched for age, sex and pre-existing comorbidity and smoking status.

Table 2 Patient characteristics expressed in number (%) unless stated otherwise of the patient group, and control group

	Patient	Control	p-value
N	54	23	
Male	33 (61.1%)	10 (42.3%)	p >0.05*
Age, mean ±SD	53.1 ±14.2	53.6 ±9.7	p >0.05$^{\$}$
Range	20-81	38-73	
Comorbidity	22 (40.7%)	9 (39.1%)	p >0.05*
Smoking status			p >0.05*
Current	24 (44.4%)	6 (26.1%)	
Former	19 (35.2%)	8 (34.8%)	
Never	11 (20.4%)	9 (39.1%)	

*Pearson chi-square $^{\$}$Mann-Whitney test

Table 3 NCSI scores on all sub-domains (the higher the score, the more problematic)

Main domain	Sub-domain	Min-max	Patient Mean ±SD	Control Mean ±SD	p-value
Symptoms	Subjective Symptoms	2-20	7.26 ±4.85	4.57 ±4.92	0.002
	Dyspnea Emotions	6-24	9.85 ±4.36	7.39 ±3.16	0.005
	Fatigue	8-56	34.35 ±13.78	23.87 ±14.08	0.004
Functional Impairment	Behavioral Impairment	0-135.5	8.21 ±11.65	3.13 ±6.37	0.050
	Subjective Impairment	4-28	9.70 ±5.55	6.00 ±3.49	<0.001
Quality of Life	General QoL	1-101.6	19.52 ±17.84	11.96 ±9.98	ns
	HRQoL	2-10	4.26 ±2.04	3.35 ±1.40	ns
	Satisfaction Relations	2-10	3.72 ±2.08	2.70 ±1.29	0.015

Mann-Whitney test , ns= not significant.

Results on the sub-domains of the NCSI on a group level are provided in Table 3. Q fever patients had significantly higher scores on all sub-domains of 'symptoms' (subjective pulmonary symptoms, dyspnea emotions, fatigue), 'functional impairment' (subjective impairment, behavioral impairment) and 'satisfaction with relations'. With respect to the main domain 'quality of life', there was a non-significant trend towards more problematic (i.e. higher) scores on the sub-domains 'general quality of life' (P= 0.09) and 'health related quality of life' (P= 0.073).

In Figure 1, results are presented on an individual level by the percentages of patients and controls scoring in the range of normal, mild, or severe problems. Fatigue scores of Q fever patients were abnormal (score: mild or severe) in 74% vs 48% in controls.

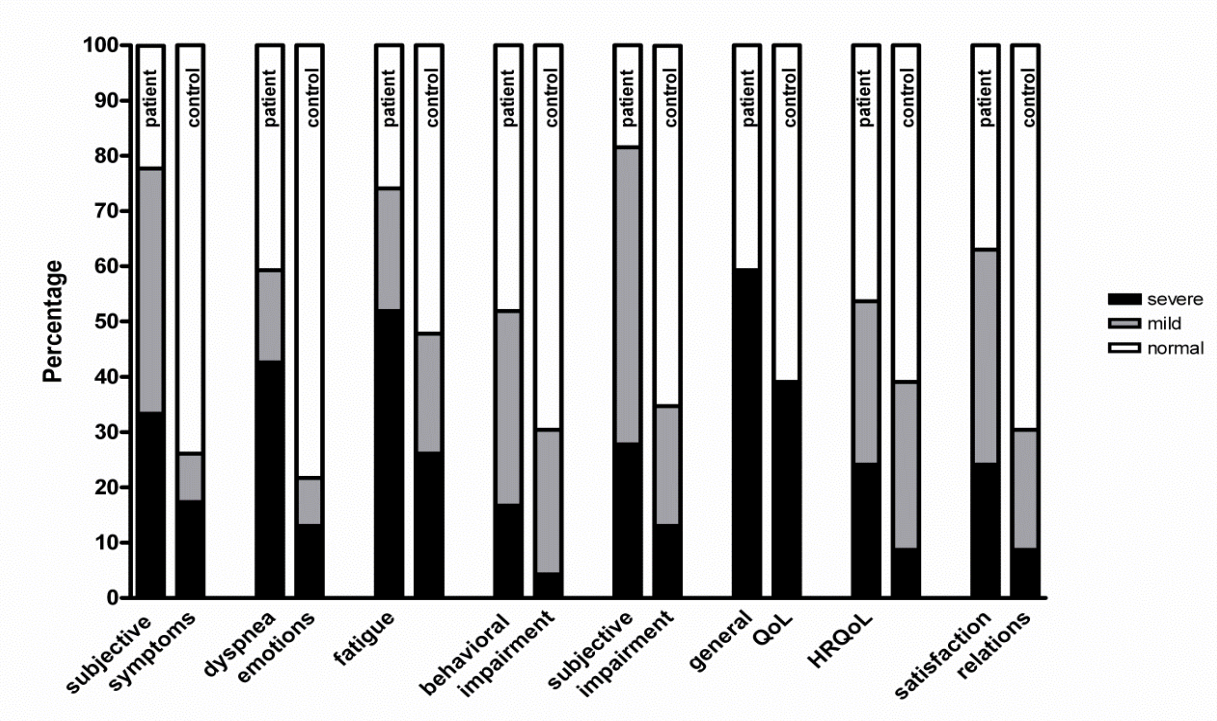


Figure 1 Percentages of normal, mild, and severe problems for each sub-domain of the NCSI for the patient and control group (*P<0.05).

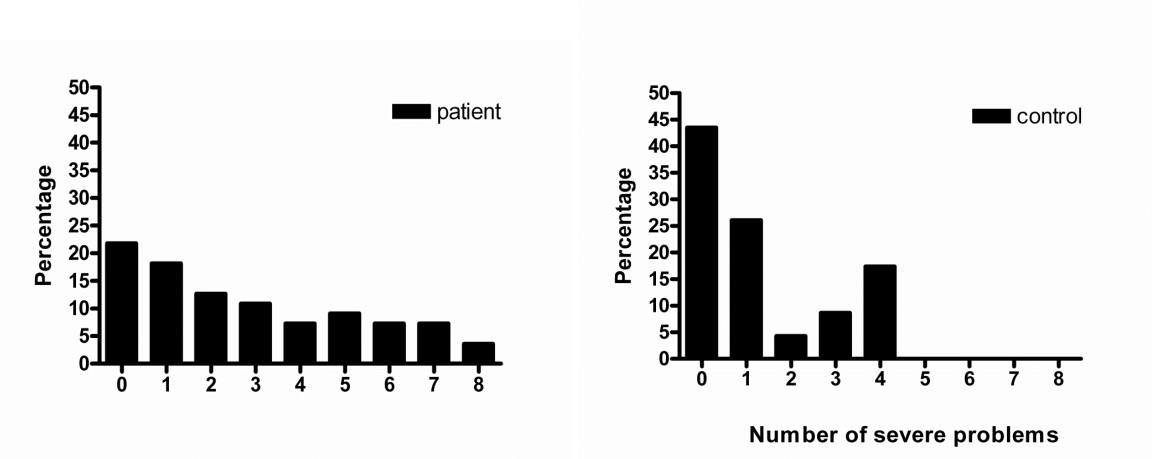


Figure 2 Frequency distribution of numbers of sub-domains with severe problems in patients and controls

Severe fatigue levels were present in 52% of patients vs. 26% in controls. Overall QoL was decreased in a substantial number of patients and controls, but not significantly different between the two groups (Q fever patients 59% vs. controls 39%, ns).

In Figure 2, the percentage of patients and controls (y-axis) is given as a function of the number of sub-domains in which these patients and controls experience severe problems (x-axis) . In addition to the primary data analysis, we compared NCSI scores of the excluded seropositive controls (n=11) with the scores of seronegative control subjects (n=23). The NCSI scores of seropositive- and seronegative controls were not statistically different in all eigth measured sub-domains of health status (P> 0.05 for all sub-domains).

DISCUSSION

One year after primary infection, Q fever patients from the 2007 Herpen outbreak had a significantly lower health status in many sub-domains of the main domains 'symptoms' and 'functional impairment', when compared to age-, sex- and geographically matched controls. Overall QoL and health-related QoL were significantly decreased in both patients and controls. Furthermore, on an individual level, patients had severe problems in more sub-domains than controls. Our findings lend support to the notion of a protracted reconvalescence phase after Q fever associated with decreased health status in many aspects.

We found remarkably high clinically relevant (=severe) fatigue levels in roughly half (52%) of the Q fever patients 1 year after infection. In two separate case control studies published as letters the editor in the Lancet in 1996, Marmion et al. [4] and Ayres et al. [5] reported a syndrome of protracted fatigue and debility in Q fever patients for >5 years after primary infection with similar fatigue levels [67% (n=39) and 66% (n=71) respectively]. Five- and 10-year follow-up of the large Q fever outbreak in the West Midlands, UK, also showed

similar levels of chronic fatigue [6, 7]. Dubbed the post Q fever fatigue syndrome (QFS), this protracted fatigue state shares common features with the chronic fatigue syndromes following other (viral) pathogens such as Epstein-Barr virus and Ross River virus [9].

Although there was a significantly higher fatigue level in Q fever patients, the abnormally high-fatigue level and low overall QoL and health-related QoL of the control group is striking. We postulate two explanations for this. First, the level of co-morbidity in this study is ~40%, which could partly account for the overall high scores on the NCSI sub-domains. Second, the original normal values for NCSI sub-domain scores were derived from healthy control subjects with normal pulmonary function tests. As these test were not available in the present study and given the significant smoking history equally present in patients and controls, undocumented pre-existing pulmonary morbidity may also have increased NCSI sub-domain scores in both groups.

Remarkably, NCSI scores from controls without a clinical history of Q fever but with serological evidence of exposure to *C. burnetii* (and thus excluded from the primary analysis), were not statistically different from seronegative controls, suggesting that clinical expression of acute Q fever infection is an essential factor in the subsequent sustained decrease in health status. Severity of initial illness previously indeed has been shown to be the best predictor of subsequent development of a post-infective fatigue syndrome in both viral and non-viral pathogens, including Q fever [9]. Moreover, the same genetic polymorphisms in cytokine genes with critical roles in the inflammatory reponse to infection, underpin both the severity of the acute sickness and the average time to recovery across varied infections, including Q fever [19].

There are obvious difficulties with the credibility of QFS as a distinct clinico-pathological entity, as confounding factors such as financial compensation or insurance benefits following the acute sickness can be held responsible for the symptomatology and associated reduced QoL. However, both the West Midlands outbreak mentioned earlier and the currently described Dutch outbreak were non-occupational and no litigation for financial compensation was pursued. A QFS diagnosis relies solely on the patient's own account of symptoms. In clinical practice, QFS patients remain indistinguishable from patients with a complete recovery after primary infection with *C. burnetii*, as they do not meet the criteria for chronic Q fever infection: anti-phase I IgG titers are less than 800 and appropriate cultures of the patients blood or tissues show no viable bacteria. Recently, an elegant new paradigm of persistence of *Coxiella* antigenic non-viable cell residues after primary infection in interaction with immunogenetic polymorphisms in the host has been put forward to better explain the chronic sequelae of acute Q fever, including QFS [20]. The importance of genetic host factors in QFS is supported by research done by Kerr et al. [21, 22] in the UK. They found significant differences in expression of 88 human genes, notably with a high proportion of genes involved in the immune response and infection, between patients with idiopathic chronic fatigue syndrome and normal controls. Remarkably, QFS patients were found to have similar patterns of gene expression to patients with idiopathic chronic fatigue syndrome.

Although our data support a decrease in many aspects of health status in many Q fever patients, some considerations have to be taken into account. First of all, patient numbers are small. However, Q fever patients were optimally matched, including serological testing in the controls. Furthermore, despite the small numbers, a statistically significant difference was found in six of the eight tested sub-domains of the NCSI, supporting the notion of a rather large difference in health status between patients and controls. Second, the NCSI has proved to be a useful tool in assessing health status for use in research and care, but has mostly been applied in COPD patients. We used the NCSI in the setting of post-infectious health status assessment for the first time. Nevertheless, the various (parts of) questionnaires used to compile the NCSI function in their original and unaltered form. These generic questionnaires are not specified to assess only pulmonary disease and assess the different sub-domains of health status in the exact same way these instruments were originally designed and validated for. Moreover, the NCSI can be used by the clinician as an excellent tool to identify and monitor health status in its various sub-domains and can even guide therapeutic (psychological) interventions.

In conclusion, these data support a sustained decrease in health status in Q fever patients in The Netherlands, one year after primary infection. With more than 3000 new Q fever patients in the last 2 years in the setting of the ongoing Dutch Q fever epidemic, these are the first clinical data indicating a major long-term burden of the disease in the years to come.

Conflict of interest: None declared.

REFERENCES

1. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infectious Diseases. 2005: 5(4):219-26.
2. Maurin M, Raoult D. Q fever. Clinical Microbiology Reviews. 1999: 12(4):518-53.
3. Fenollar F, Fournier PE, Carrieri MP, Habib G, Messana T, Raoult D. Risks factors and prevention of Q fever endocarditis. Clinical Infectious Diseases. 2001: 33(3):312-6.
4. Marmion BP, Shannon M, Maddocks I, Storm P, Penttila I. Protracted debility and fatigue after acute Q fever. Lancet. 1996: 347:977-8.
5. Ayres JG, Smith EG, Flint N. Protracted fatigue and debility after acute Q fever. Lancet. 1996: 347(9006):978-9.
6. Ayres JG, Flint N, Smith EG, Tunnicliffe WS, Fletcher TJ, Hammond K, Ward D, Marmion BP. Post-infection fatigue syndrome following Q fever. QJM: an international journal of medicine. 1998: 91(2):105-23.
7. Wildman MJ, Smith EG, Groves J, Beattie JM, Caul EO, Ayres JG. Chronic fatigue following infection by Coxiella burnetii (Q fever): ten-year follow-up of the 1989 UK outbreak cohort. QJM: an international journal of medicine. 2002: 95(8):527-38.

8. Hatchette TF, Hayes M, Merry H, Schlech WF, Marrie TJ. The effect of C. burnetii infection on the quality of life of patients following an outbreak of Q fever. Epidemiology and Infection. 2003: 130(3):491-5.
9. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006: 333(7568):575.
10. Raoult D. Q fever: still a mysterious disease. QJM: an international journal of medicine. 2002: 95(8):491-2.
11. Van Steenbergen JE, Morroy G, Groot CA, Ruikes FG, Marcelis JH, Speelman P. [An outbreak of Q fever in The Netherlands--possible link to goats]. Nederlands Tijdschrift voor Geneeskunde. 2007: 151(36):1998-2003.
12. Schimmer B, Morroy G, Dijkstra F, Schneeberger PM, Weers-Pothoff G, Timen A, Wijkmans C, van der Hoek W. Large ongoing Q fever outbreak in the south of The Netherlands, 2008. Euro Surveillance. 2008: 13(31).
13. Schimmer B, Dijkstra F, Vellema P, Schneeberger PM, Hackert V, ter Schegget R, Wijkmans C, van Duynhoven Y, van der Hoek W. Sustained intensive transmission of Q fever in the south of the Netherlands, 2009. Euro Surveillance. 2009: 14(19).
14. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. Journal of the American Medical Association. 1995: 273:59-65.
15. Taillefer SS, Kirmayer LJ, Robbins JM, Lasry JC. Psychological correlates of functional status in chronic fatigue syndrome. Journal of Psychosomatic Research. 2002: 53(6):1097-106.
16. Vercoulen JH, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavioral Medicine. 2008: 15(4):263-79.
17. Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. Quality of Life Research. 2009: 18(7):901-12.
18. Vercoulen JHMM, Swanink CMA, Galama JMD et al. Dimensional assessment in chronic fatigue syndrome. Journal of Psychosomatic Research. 1994: 38:383-392.
19. Vollmer-Conna U, Piraino BF, Cameron B, Davenport T, Hickie I, Wakefield D, Lloyd AR. Cytokine polymorphisms have a synergistic effect on severity of the acute sickness response to infection. Clinical Infectious Diseases 2008: 47(11):1418-25.
20. Marmion BP, Sukocheva O, Storm PA, Lockhart M, Turra M, Kok T, Ayres J, Routledge H, Graves S. Q fever: persistence of antigenic non-viable cell residues of Coxiella burnetii in the host--implications for post Q fever infection fatigue syndrome and other chronic sequelae. QJM: an international journal of medicine. 2009: 102(10):673-84.
21. Kerr JR, Petty R, Burke B, Gough J, Fear D, Sinclair LI, Mattey DL, Richards SC, Montgomery J, Baldwin DA, Kellam P, Harrison TJ, Griffin GE, Main J, Enlander D, Nutt DJ, Holgate ST. Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. Journal of Infectious Diseases. 2008: 197(8):1171-84.
22. Zhang L, Gough J, Christmas D, Mattey DL, Richards SC, Main J, Enlander D, Honeybourne D, Ayres JG, Nutt DJ, Kerr JR. Microbial infections in eight genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis. Journal of Clinical Pathology. 2010: 63(2):156-64.

CHAPTER 8

General discussion

Several questionnaires have been developed to measure impaired health and well-being in patients with COPD. Although research using these questionnaires has provided important information about patients with COPD, it has also raised new questions. While the choice of questionnaire is often based on which questionnaires are commonly used, it is not always clear what questionnaires actually measure. The conceptual confusion regarding terms such as health status, quality of life, health-related quality of life, etcetera has played a major role in this. This is illustrated by the fact that questionnaires that are assumed to measure different concepts show overlap, and that questionnaires said to measure the same concept yield different results [1]. Moreover, the same questionnaire is used in one study to measure quality of life and in another study to measure health status or health-related quality of life, depending on what is 'hot' at that moment. By using different terms for the same questionnaire it is unclear which concept is being evaluated. In research, but especially in clinical care, it is important to know what is measured and what the results imply. If these questions cannot be answered, then it is questionable whether the use of these instruments is of added value to the individual patient.

Already in 1997, a round table conference concluded that it would be better to improve existing questionnaires rather than develop new ones [1]. The authors recommended comparison of existing instruments to identify the best instrument, standardization of terminology, and improvement of the validity and interpretability of the instruments, with a view to improving and standardizing the measurement of health status in research and in clinical practice. However, since then several instruments have been developed for COPD, such as the COPD Assessment Test (CAT) to measure COPD health status [2] and the Clinical COPD Questionnaire (CCQ) to measure symptoms and functional state [3], and the conceptual confusion remains.

Questionnaire validation is a difficult process. The traditional validation approach for a new questionnaire is to correlate questionnaire data with those of an existing questionnaire assumed to measure a particular concept. However, there are several problems to this approach in the case of health status and quality of life. First, there are multiple definitions of health status and quality of life. Second, no gold standard exists for highly subjective concepts such as quality of life, and so the validity of the questionnaire that is used as a reference in this process is also unclear. Our research group used a different approach when developing the Nijmegen Integral Assessment Framework (NIAF) [4]. Questionnaires and tests were selected on the basis of theoretical models found in the literature and were used to collect data from a group of outpatients with COPD. These data were analyzed, by factor analysis, to establish what the questionnaire measured, instead of making assumptions about what it measures. This enabled tests and questionnaires that measured the same concept to be grouped together, with subscales of questionnaires that measure different aspects of integral health status being classified in different sub-domains. This resulted in the NIAF, which provides an overview by organizing tests and questionnaires according to what aspects, physiological functioning, symptoms, functional impairment, or quality of life, they actually measure [4]. This framework brings greater clarity to the

measurement of integral health status in several ways. For instance, the NIAF can be used as standard to examine what a questionnaire measures, by comparing it with included questionnaires, and it provides an overview of what sub-domains are measured by the included tests and questionnaires. It can also be used as guide to select tests and questionnaires to measure certain sub-domains of integral health status.

Using the NIAF, we could show that integral health status covers at least sixteen relatively unrelated sub-domains that cannot be measured with currently available individual instruments. This makes it necessary to use a combination of instruments to measure a patient's integral health status. The Nijmegen Clinical Screening Instrument (NCSI) was developed with this in mind (chapter 3), by combining subscales from existing questionnaires for each sub-domain of the NIAF. In this way, various aspects of integral health status are covered with as little overlap as possible. For use in clinical care, it was necessary to remove five of the sixteen sub-domains as these took too much time to complete. Even so, the NCSI measures more aspects of integral health status than most other frequently used (disease-specific) questionnaires. By using the NIAF as golden standard for the selection of items to measure health status, no question about what is actually measured by the NCSI exists, and it is also apparent what is not measured by the NCSI.

In research, the St George Respiratory Questionnaire (SGRQ) [5], the Asthma Control Questionnaire (ACQ) [6, 7], and the Asthma Quality of Life Questionnaire (AQLQ) [8] are disease-specific questionnaires that are used the most often to measure quality of life or health-related quality of life in patients with COPD and asthma. The SGRQ is sometimes also used to measure health status. Comparison of the SGRQ with the NIAF (chapter 4) and the ACQ and AQLQ with the NCSI (chapter 6) showed that these instruments have relatively little conceptual similarity with the NCSI sub-domains. The SGRQ, ACQ, and AQLQ showed conceptual similarity with the NCSI sub-domains subjective symptoms and subjective impairment, and the AQLQ additionally with dyspnea emotions. Moreover, the three questionnaires definitely do not measure any aspect of quality of life, as defined in this thesis (chapter 1). The recently developed CAT and CCQ have been shown to be conceptually similar to each other and to the SGRQ (correlations between 0.64-0.77) [9-11], thus presumably these instruments also only measure two aspects of functional impairment and symptoms. Regardless of how important these sub-domains are, health status encompasses more sub-domains than those measured by the ACQ, AQLQ, and SGRQ. Hence integral health status cannot be measured with these instruments alone.

Another shortcoming of many questionnaires is the interpretability of the scores. In general, the higher (or lower) the score, the more problems on that aspect exist. However, normality cannot be defined by the absence of symptoms of impairment. For example, healthy people also experience fatigue (Chapter 2). For this reason, we collected reference data for each sub-domain of the NCSI, to improve the interpretability of findings, both in research and clinical settings. Instead of only providing mean scores, information is also available about, for example, how many patients experience severe problems on specific

sub-domains. Moreover, it can be seen on which sub-domains of integral health status the patient functions normally or has problems. Results are visualized for patients and clinicians in the PatientProfileChart, using different colors (green, yellow, and red) for greater clarity. In this way, patients are given verbal and visual feedback of information, which minimizes the chance that there are misunderstandings and facilitates discussion. Also possible discrepancies between sub-domains are visible and subject for discussion. Discussing results and potential treatments with patients improves their commitment and treatment adherence and can lead to better results with patient-tailored treatment.

One of the goals of patient-tailored treatment in COPD is to optimize and/or maintain the patient's integral health status [12, 13]. Many treatment modalities aim at teaching patients adequate self-management strategies, such as adherence to medication regimens, exacerbation management, stopping smoking, taking regular exercise, energy-saving strategies, breathing regulation, stress management, and so on. All these self-management strategies need to be adopted in daily life and most important require behavioral change [14, 15]. However, some patients report more symptoms, functional impairments, and quality of life issues than one would expect on the basis of their disease severity, and it is these patients who tend not to implement self-management strategies in daily life. This may be for several reasons. Patients need to acknowledge that COPD is a chronic and progressive disease, which requires changes in daily life, but if patients do not think that this will be beneficial, then they tend not to make behavioral changes. In turn, clinicians need to be able to recognize which patients do not adequately adapt to the disease. Awareness of the necessity and motivation to change behavior are necessary ingredients for adaptation. It is important to establish whether certain patients can be helped to adapt to their disease, which would improve their integral health status. The first step is to identify the patient's level of adaptation to COPD.

It is difficult to define adaptation to disease and how to assess it. For example, while physical activity should be discouraged in some patients, it should be encouraged in others. We took a different approach to assessing adaptation, on the assumption that patients who are not adequately adapted to their disease experience more symptoms, functional impairment, and lower quality of life than would be expected on the basis of their disease severity. In patients who have adapted to their disease, the four domains of health status are in balance, but not in other patients. If these differences exist, then it might be possible to identify different groups of patients with COPD by cluster analyses (chapter 5). Indeed, two clinical phenotypes were found in which physiological functioning, symptoms, functional impairments, and quality of life were in balance, and one clinical phenotype was found with more reported symptoms, greater functional impairment, and poorer quality of life, all of which were not consistent with the FEV_1% predicted. We then investigated whether these profiles really reflected the level of adaptation, by examining the effect of pulmonary rehabilitation on the three clinical phenotypes. One of the goals of pulmonary rehabilitation is to stimulate adaptation to the disease by promoting self-efficacy and behavior change [16]. We expected that rehabilitation would be most effective in patients with the 'not

adapted' clinical phenotype and perhaps less effective in patients with the 'adapted' clinical phenotype, especially because the latter reported no or lower levels of symptoms, functional impairment, and quality of life. As expected, pulmonary rehabilitation had the greatest effect in the 'not adapted' patients expressed by a better balance between the four domains of integral health status at the end of rehabilitation. Understanding what type of treatment works and what type does not in specific clinical groups of patients will help clinicians to choose potentially effective treatments for specific patients. It is important to appreciate that identifying a patient's clinical phenotype is not a substitute for identifying the patient's individual profile, but is an aid to facilitate appropriate tailored treatment.

In this thesis, the definition of integral health status was based on theoretical models, such as the model of Wilson and Cleary [17], which has also been shown to fit other diseases such as HIV [18], Hodgkin's lymphoma [19], and Parkinson's disease [20]. Independent of the type of disease, integral health status minimally covers the domains physiological functioning, symptoms, functional impairment, and quality of life. How these domains are measured depends partly on the characteristics of a given disease. For example, the lung function test provides important information about the severity of COPD, but has no added value in many other diseases. However, beside disease-specific aspects, integral health status also encompasses generic aspects, such as general quality of life. The NCSI incorporates disease-specific and generic instruments that, in theory, should be applicable to other patient groups with respiratory symptoms. If this hypothesis is correct, it would make it possible to compare different disease groups. In addition, the PatientProfileChart with cut-off scores could help guide treatment choices in other diseases. The studies involving patients with asthma (chapter 6) and patients with Q-fever (chapter 7) showed that the various sub-domains of the NCSI are also relevant in these patient groups. For all sub-domains, a certain proportion of patients were found to have normal or raised levels or clinically relevant problems. These groups shared some characteristics but differed in others. For example, in both groups fatigue and poor general quality of life were clinically relevant problems, but whereas a large proportion of patients with asthma experienced subjective impairments and subjective symptoms, this was not the case for patients with Q-fever. Thus while the generic part of the NCSI can probably be used for other diseases, it might be necessary to make adaptations with regard to the level of symptoms and physiological measures.

Future research

The aim of the studies described in this thesis was to clarify the assessment of integral health status in individual chronically ill patients – what should be measured and how it should be measured. While some questions were answered, new ones arose.

Fatigue was not originally incorporated in the NIAF (chapter 2), and it is possible that other sub-domains of physiological functioning, symptoms, functional impairment, or quality of life also merit inclusion in the NIAF and the NCSI. Open semi-structured interviews with patients might provide new important information about topics that are currently not

assessed. It is then a question of collecting and analyzing data and establishing reference data. This is also true if the NIAF and NCSI are to be used for other diseases.

The NCSI was developed for use in both research and clinical settings, to gain a detailed picture of a patient's integral health status, to identify problems early. While it was originally intended to repeat this screening every year, results (*chapter 5*) showed that in most patients there are no clinically relevant changes in a year. Since the NCSI takes 20 minutes to complete, it might be more of a burden than a benefit to patients. More research is needed to find the appropriate time frame for screening, bearing in mind that the optimal timing of screening may vary between patients depending on the specific problems they experience. Another point that needs attention is the relevance of screening. It is intended to help clinicians make treatment choices, but this has yet to be confirmed in daily practice.

The identification of the three clinical phenotypes that each responded differently to treatment seem to be an important addition to the NCSI, but needs to be validated in clinical practice, as existing datasets were used in the study described in chapter 5. Future research should investigate whether knowing how well a patient is adapted to his or her disease influences the choice of treatment to optimize that patient's integral health status. In addition, more needs to learned about whether other types of treatment beside pulmonary rehabilitation influence the integral health status of the three clinical phenotypes. Understanding what type of treatment works and what type does not in specific clinical phenotypes will help clinicians select effective treatments for each clinical phenotype.

At the moment, the NCSI has proven useful in research studies involving patients with Q-fever [21-24](chapter 7), asthma (chapter 6), and cardiac diseases (submitted). The next step is to implement the NCSI with the PatientProfileChart in clinical practice for these diseases. It would be interesting to examine whether comparable clinical phenotypes can be identified in these patient groups, since adaptation to disease is not exclusive to COPD.

Clinical implications

Concepts are often used in research and clinical practice without there being a clear understanding of what these concepts entail – not everyone uses the same definitions for concepts. What is quality of life to one person, is health status to another. Thus to avoid conceptual confusion, concepts should be defined when they are used.

The NCSI was developed for both research purposes and clinical use. One advantage of using a standardized instrument in daily practice is that in a short time many questions are answered and the same information is available for each patient. Time constraints, and the burden and benefit to patients are factors that influence what it is reasonable to assess in clinical care. The NCSI takes about 20 minutes to complete and provides a detailed picture of a patient's integral health status (PatientProfileChart). This profile provides information about problem areas and makes discrepancies visible to both physician and patient. Discussion of the PatientProfileChart with the patient has proven very effective – problems were detected early, before they exacerbated, so that treatment could be started in a timely fashion. Ideally, this method should be implemented for screening and monitoring in all

centers dealing with patients with COPD. However, standard assessment with the NCSI might be too time consuming and some patients experience no problems. For these reasons, a short screening instrument with the simple outcome 'yes, more assessment is needed' or 'no, more assessment is not needed' was developed, based on the NCSI. This screening instrument identifies patients who experience problems in their integral health status and who need detailed assessment. In this way, many patients can be easily screened in daily clinical practice.

REFERENCES

1. Curtis JR, Martin DP, Martin TR. Patient-assessed health outcomes in chronic lung disease: what are they, how do they help us, and where do we go from here? American Journal of Respiratory and Critical Care Medicine 1997: 156:1032-1039.
2. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. European Respiratory Journal 2009: 34(3): 648-654.
3. van der Molen T, Willemse BW, Schokker S, ten Hacken NH, Postma DS, Juniper EF. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health and Quality of Life Outcomes 2003: 1:13.
4. Vercoulen, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). International Journal of Behavior and Medicine 2008: 15(4):263-279.
5. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respiratory Medicine 1991: 85 Suppl B: 25-31;discussion 33-27.
6. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. European Respiratory Journal 1999: 14(4):902-907.
7. Juniper EF, Bousquet J, Abetz L, Bateman ED, Committee G. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respiratory Medicine 2006: 100(4):616-621.
8. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999: 115(5):1265-1270.
9. Miravitlles M, Garcia-Sidro P, Fernandez-Nistal A, Buendia MJ, Espinosa de los Monteros MJ, Molina J. Course of COPD assessment test (CAT) and clinical COPD questionnaire (CCQ) scores during recovery from exacerbations of chronic obstructive pulmonary disease. Health and Quality of Life Outcomes 2013: 11:147.
10. Ringbaek T, Martinez G, Lange P. A comparison of the assessment of quality of life with CAT, CCQ, and SGRQ in COPD patients participating in pulmonary rehabilitation. COPD 2012: 9(1):12-15.
11. Tsiligianni IG, van der Molen T, Moraitaki D, Lopez I, Kocks JW, Karagiannis K, Siafakas N, Tzanakis N. Assessing health status in COPD. A head-to-head comparison between the COPD assessment test (CAT) and the clinical COPD questionnaire (CCQ). BMC pulmonary medicine 2012: 12:20.
12. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014. 2014; Available from: http://www.goldcopd.org/
13. Nici L, ZuWallack R, American Thoracic Society Subcommittee on Integrated Care of the CP. An official American Thoracic Society workshop report: the Integrated Care of The COPD Patient. Proceedings of the American Thoracic Society 2012: 9(1):9-18.

14. Effing TW, Bourbeau J, Vercoulen J, Apter AJ, Coultas D, Meek P, Valk P, Partridge MR, Palen J. Self-management programmes for COPD: moving forward. Chronic Respiratory Disease 2012: 9(1):27-35.
15. Vercoulen. A simple method to enable patient-tailored treatment and to motivate the patient to change behavior. Chronic Respiratory Disease2012: In press.
16. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Molken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF, Rehabilitation AETFoP. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine 2013: 188(8):e13-64.
17. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patients outcomes. Journal of the American Medical Association 1995: 273 59-65.
18. Sousa KH, Kwok OM. Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. Quality of Life Research 2006: 15(4):725-737
19. Wettergren L, Bjorkholm M, Axdorph U, Langius-Eklof A. Determinants of health-related quality of life in long-term survivors of Hodgkin's lymphoma. Quality of Life Research 2004: 13(8):1369-1379.
20. Chrischilles EA, Rubenstein LM, Voelker MD, Wallace RB, Rodnitzky RL. Linking clinical variables to health-related quality of life in Parkinson's disease. Parkinsonism & related disorders 2002: 8(3):199-209.
21. Morroy G, Peters JB, van Nieuwenhof M, Bor HH, Hautvast JL, van der Hoek W, Wijkmans CJ, Vercoulen JH. The health status of Q-fever patients after long-term follow-up. BMC Infectious Diseases 2011: 11:97.
22. van Loenhout JA, Paget WJ, Sandker GW, Hautvast JL, van der Velden K, Vercoulen JH. Assessing health status and quality of life of Q-fever patients: the Nijmegen Clinical Screening Instrument versus the Short Form 36. Health and Quality of Life Outcomes 2013: 11(1):112.
23. van Dam AS, van Loenhout JA, Peters JB, Rietveld A, Paget WJ, Akkermans RP, Olde Loohuis A, Hautvast JL, van der Velden J. A cross-sectional study to assess the long-term health status of patients with lower respiratory tract infections, including Q fever. Epidemiology and infection 2014:1-7.
24. van Loenhout JA, van Tiel HH, van den Heuvel J, Vercoulen JH, Bor H, van der Velden K, Paget WJ, Hautvast JL. Serious long-term health consequences of Q-fever and Legionnaires' disease. Journal of Infection 2014. In press

SUMMARY

In this thesis, we focused on the assessment of integral health status in patients with chronic lung diseases. On the basis of theoretical models and clinical considerations, we defined concepts, selected tests and instruments, and empirically tested these in a group of patients with Chronic Obstructive Pulmonary Disease (COPD). Factor analysis revealed that integral health status encompasses at least four domains: physiological functioning, symptoms, functional impairment, and quality of life. These four domains can be subdivided into several sub-domains, all of which are relatively unrelated to each other, so that each sub-domain reflects a unique aspect of integral health status. This means that these different aspects all need to be measured in order to get a complete picture of a patient's integral health status. The development of an instrument that measures the integral health status of patients with COPD, its use in daily clinical practice, and its usefulness in other chronic diseases were the three main subjects of this thesis.

Chapter 2

Given that patients with COPD report fatigue as the second most important symptom after dyspnea, it is remarkable that fatigue has not gained much attention in COPD research and especially not in clinical practice. In the study reported in Chapter 2, the prevalence and natural course of 'normal' and 'abnormal' fatigue and the relationship between fatigue and the many sub-domains of integral health status were investigated in patients with COPD. Results showed that more than half of the patients reported abnormal fatigue, and after four years a clinically relevant increase in fatigue was observed in one third of the patients. Patients with abnormal fatigue had a significantly lower exercise capacity and had more symptoms, a greater functional impairment (except actual daily activity), and a poorer quality of life than patients with normal levels of fatigue. Analysis showed that fatigue and dyspnea are conceptually distinct and that both measure a unique aspect of integral health status. Therefore fatigue has to be measured in order to get a complete picture of a patient's integral health status. Accordingly, fatigue was incorporated as an additional sub-domain in the Nijmegen Integral Assessment Framework (NIAF), within the main domain symptoms.

Chapter 3

Since treatment goals have expanded from merely optimizing physiological functioning to optimizing patients' integral health status, there is a need for an instrument that measures the integral health status of patients. This instrument should be suitable for use in both research and clinical settings. For use in daily clinical practice, it is essential that this instrument is short and easy to complete and score, and that results are easy to interpret. In particular, results should be clinically meaningful with respect to the individual patient. In the study described in Chapter 3, a battery was developed of existing questionnaires that fulfill the above-mentioned criteria: the Nijmegen Clinical Screening Instrument (NCSI). The comprehensive Nijmegen Integral Assessment Framework (NIAF) was used as 'gold standard'

for the selection of subscales for the sub-domains. Cut-off scores for normal functioning and severe problems in the sub-domains were established using data for age and sex-matched healthy controls and patients who were enrolled in an inpatient pulmonary rehabilitation program. To enhance the clinical applicability of this instrument, computer software was developed to present results in a graph, the PatientProfileChart, immediately after assessment. The PatientProfileChart provides a visual presentation of the results in green-yellow-red 'traffic light' bars (see figure 1, chapter 3). The software makes it also possible to complete the questionnaire at home and avoids missing values by not allowing to skip items. The NCSI in combination with the PatientProfileChart provides a detailed picture of a patient's integral health status and indicates problem areas and discrepancies between the diverse sub-domains.

Chapter 4

The St. George Respiratory Questionnaire (SGRQ) is one of the most frequently used questionnaires in COPD research. The SGRQ is variously assumed to measure health-related quality of life, quality of life, or health status. Although these terms and definitions are used interchangeably in the literature, the different terms refer to different concepts, as pointed out in the Introduction. In order to interpret data, it is important to know what exactly is measured with the sections Symptoms, Activity, and Impact of the SGRQ. This was addressed in the study reported in Chapter 4. Comparison of the SGRQ with eleven non-physiological sub-domains of the NIAF revealed that the SGRQ sections measure only subjective impairment and subjective symptoms, especially dyspnea. Thus, the SGRQ measures only two aspects of integral health status and therefore does not provide a complete picture. Most importantly, we found that the SGRQ does not measure quality of life or health-related quality of life.

Chapter 5

In recent years, several phenotypes of COPD have been identified, based on physiological and pathological parameters that respond differently to pharmacological treatment. Not only pulmonary and extra-pulmonary manifestations of COPD, but also their impact on health status differ between patients. In clinical practice, some patients report more symptoms, functional impairments, and lower quality of life than would be expected on the basis of the results of physiological tests, and vice versa. Adaptation to the disease is assumed to play an important role in this observed discrepancy. In the study reported in this chapter, we identified three clinical phenotypes, based on a variety of parameters measuring aspects of integral health status, which reflected the level of adaptation to COPD. A secondary aim was to examine whether these clinical phenotypes respond differently to care as usual and to an inpatient pulmonary rehabilitation program, which has a strong focus on improving adaptation to disease. Health status did not improve in any of the three

phenotype groups after one year of care as usual; however, there were intergroup differences after the inpatient pulmonary rehabilitation program. Whereas the 'adapted' phenotypes showed significant improvements in four to six sub-domains, the 'non-adapted' phenotype showed significant improvements in ten of eleven sub-domains of integral health status. These improvements resulted in a better balance between the four domains of health status, indicating better adaptation. Thus knowing a patient's clinical phenotype will help clinicians to optimize patient-tailored treatment.

Chapter 6

The NCSI was developed on the basis of data from patients with COPD. As the NCSI includes both generic and disease-specific instruments to measure the integral health status, it is plausible that the instrument can also be used for other diseases with respiratory symptoms. The relevance of the NCSI was evaluated in a group of patients with severe asthma, by comparing it with the internationally most frequently used asthma questionnaires, the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ). All sub-domains of the NCSI identified a substantial proportion of patients with severe problems, indicating that all sub-domains are relevant in patients with asthma. The NCSI sub-domains subjective symptoms, fatigue, subjective impairment, and general quality of life identified the highest proportion of patients with severe problems. There was also heterogeneity in the number of sub-domains in which patients had severe problems. The ACQ showed conceptual similarity with two of eight sub-domains of the NCSI, namely, subjective symptoms and subjective impairment. The AQLQ showed conceptual similarity with three of eight sub-domains of the NCSI, namely, subjective symptoms, subjective impairment, and dyspnea emotion. In contrast to the other subscales of the AQLQ, the subscale environmental stimuli measured an aspect of integral health status not measured with the NCSI. However, neither the ACQ nor the AQLQ measured any aspect of quality of life. On the basis of these results, it can be concluded that the NCSI measures more sub-domains of integral health status that are relevant to patients with severe asthma. In particular, some highly relevant aspects, such as fatigue and general quality of life, are not covered by the ACQ and AQLQ.

Chapter 7

In 2007 there was an outbreak of Q-fever in the Netherlands. The study described in Chapter 7 evaluated the integral health status of patients with Q-fever one year after the outbreak in comparison with age- and sex-matched controls not affected by Q-fever. In both groups, a proportion of the participants had normal, mild, or severe problems on all sub-domains of the NCSI. However, patients who had positive Q-fever serology reported more problems in the domains symptoms and functional impairment than did the control participants. Fatigue was especially a prominent symptom in the patients with Q-fever. Unexpectedly, the control

participants also experienced a poor general quality of life, health-related quality of life, and fatigue. Many patients still had an impaired integral health status one year after the infection. It is important to monitor the integral health status of patients with Q-fever in order to tailor healthcare interventions with a view to limiting or preventing long-term consequences.

Chapter 8

The various studies of this thesis were discussed and new research questions and clinical implications were formulated in this chapter. Central to this thesis was the question why and how integral health status should be measured in individual patients. Chronic disease affects the whole person, not just the physiological system involved. This justifies the measurement of more than only physiological parameters. The studies showed that integral health status encompasses many relatively independent sub-domains of physiological functioning, symptoms, functional impairment, and quality of life, which all have to be measured to provide a complete picture of a patient's integral health status. This was possible with the NCSI. Moreover, although the NCSI was developed for patients with COPD, it proved useful for patients with other chronic (lung) diseases. The presentation of the results of the NCSI in a PatientProfileChart makes it easier to discuss findings with patients and helps guide patient-tailored treatment. It is essential to determine to what extent patients adapt to their disease, as this proved to be an important determinant of integral health status.

SAMENVATTING

In dit proefschrift ligt de focus op het meten van de integrale gezondheidstoestand van patiënten met een chronische longziekte. Gebaseerd op theoretische modellen en klinische overwegingen zijn concepten gedefinieerd, werden testen en instrumenten geselecteerd en empirisch getoetst in een groep patiënten met Chronic Obstructive Pulmonary Disease (COPD). Factor analyses lieten zien dat de integrale gezondheidstoestand op zijn minst vier domeinen bevat: fysiologisch functioneren, symptomen, functionele beperkingen en kwaliteit van leven. Deze vier domeinen kunnen elk onderverdeeld worden in verschillende subdomeinen die allemaal relatief ongerelateerd zijn. Dat wil zeggen dat elk subdomein een uniek aspect van de integrale gezondheidstoestand reflecteert. Deze bevinding duidt de noodzaak tot het meten van alle aspecten aan, om zo tot een compleet beeld van de integrale gezondheidstoestand van de patiënt te komen. De ontwikkeling van een instrument dat de integrale gezondheidstoestand van patiënten met COPD meet, de toepassing in de dagelijkse praktijk en de bruikbaarheid bij andere chronische ziekten zijn de drie hoofd onderwerpen van dit proefschrift.

Hoofdstuk 2

Gegeven dat patiënten met COPD moeheid rapporteren als het tweede belangrijke symptoom na benauwdheid, is het opvallend dat moeheid weinig belangstelling heeft gehad in COPD onderzoek en in de klinische praktijk. In de studie beschreven in hoofdstuk 2 zijn de prevalentie en het natuurlijk beloop van ‘normale’ en ‘abnormale’ moeheid en de relatie tussen moeheid en veel subdomeinen van de integrale gezondheidstoestand onderzocht in patiënten met COPD. De resultaten lieten zien dat meer dan de helft van de patiënten abnormale moeheid rapporteerde, en na vier jaar een klinisch relevante toename in moeheid kon worden geobserveerd in meer dan een derde van de patiënten. Patiënten met abnormale moeheid hadden een significant lager inspanningsvermogen en rapporteerden meer symptomen, meer functionele beperkingen (m.u.v. de gemeten dagelijkse activiteit) en slechtere kwaliteit van leven in vergelijking met patiënten met een normaal moeheidsniveau. Analyses lieten zien dat moeheid en benauwdheid conceptueel verschillend zijn en beide unieke aspecten van de integrale gezondheidstoestand meten. Om een compleet beeld van de patiënt zijn/haar integrale gezondheidstoestand te krijgen moet moeheid ook gemeten worden. Zodoende is moeheid geïmplementeerd als een aanvullend subdomein in het Nijmegen Integral Assessment Framework (NIAF), binnen het hoofddomein symptomen.

Hoofdstuk 3

Doordat de behandeldoelen verbreed zijn van het optimaliseren van voornamelijk fysiologisch functioneren naar het optimaliseren van de patiënt’s integrale gezondheidstoestand ontstond de noodzaak voor een instrument dat de problemen in de patiënt’s integrale gezondheidstoestand meet. Dit instrument moet zowel gebruikt kunnen

worden voor onderzoeksdoeleinden als ook in de dagelijkse zorg. Voor het gebruik in de dagelijkse praktijk is het essentieel dat het instrument kort, makkelijk in te vullen en scoren is en dat de resultaten makkelijk te interpreteren zijn. Het belangrijkste is dat de resultaten klinische waarde hebben op het niveau van de individuele patiënt. In de studie beschreven in hoofdstuk 3 werd een batterij van bestaande vragenlijsten samengesteld dat voldoet aan alle bovenstaande criteria samengesteld: het Nijmegen Clinical Screening Instrument (NCSI). Het uitgebreide Nijmegen Integral Assessment Framework (NIAF) is als 'gouden standaard ' gebruikt voor de selectie van subschalen van de subdomeinen. Cut-off scores voor normaal functioneren en ernstige problemen werden verzameld in een op leeftijd en geslacht ge-matchte groep van gezonde controles en een groep patiënten die een klinisch longrevalidatie programma volgden. Om de klinische toepasbaarheid te vergroten werd computer software ontwikkeld om zo de beschikbaarheid van de resultaten in een PatiëntenProfielKaart (PPK) meteen na afname van de vragenlijst mogelijk te maken. De PatientenProfielKaart biedt een visuele presentatie aan van de resultaten in groen-geel-rode 'stoplicht' grafieken (zie Figuur 1 hoofdstuk 3). Daarnaast maakt de software het mogelijk om de vragenlijst thuis in te vullen en worden missende waarden voorkomen doordat er geen vragen overgeslagen kunnen worden. Het NCSI in combinatie met de PatientenProfielKaart bieden een gedetailleerd beeld van de integrale gezondheidstoestand van de patiënt en indiceert probleem gebieden en discrepanties tussen de diverse subdomeinen.

Hoofdstuk 4

De St George Respiratory Questionnaire (SGRQ) is een van de meest gebruikte vragenlijsten in COPD onderzoek. Van de SGRQ wordt afwisselend aangenomen dat het de gezondheidsgerelateerde kwaliteit van leven, kwaliteit van leven of de gezondheidstoestand meet. Alhoewel deze termen en definities door elkaar gebruikt worden in de literatuur referen deze verschillende termen naar verschillende concepten zoals in de introductie is uitgelegd. Voor de interpretatie van de resultaten is het van belang te weten wat er nu precies gemeten wordt met de secties symptomen, activiteit en impact van de SGRQ. In hoofdstuk 4 werd deze vraag onderzocht. De vergelijking van de SGRQ met de elf niet fysiologische subdomeinen van het NIAF lieten zien dat de SGRQ secties alleen subjectieve beperkingen en subjectieve symptomen, met name benauwdheid, meten. Dus de SGRQ meet maar twee aspecten van de integrale gezondheidstoestand, en biedt dus geen compleet beeld. Nog belangrijker, de SGRQ blijkt niet de kwaliteit van leven of gezondheidsgerelateerde kwaliteit van leven te meten.

Hoofdtsuk 5

In de afgelopen jaren zijn verschillende phenotypes geïdentificeerd in COPD die gebaseerd zijn op fysiologische en pathologische parameters. Deze phenotypes bleken verschillend op

farmacologische behandeling te reageren. Niet alleen de pulmonaire en extra-pulmonaire manifestaties van COPD, maar ook hun impact op de gezondheidstoestand verschilt per persoon. In de klinische praktijk rapporteert een patient soms meer symptomen, functionele beperkingen en een lagere kwaliteit van leven dan verwacht zou worden op basis van de resultaten op fysiologische testen en vice versa. Adaptatie aan de ziekte lijkt een belangrijke rol te spelen in deze geobserveerde discrepancie. In de studie beschreven in dit hoofdstuk identificeerden we drie klinische phenotypes, gebaseerd op een variatie van parameters die aspecten van de gezondheidstoestand meten, welke de mate van adaptatie aan COPD reflecteerden. Het tweede doel was om te onderoeken of deze klinische phenotypes verschillend reageren op gebruikelijke zorg en op een klinische longrevalidatie, welke een sterke focus heeft op het verbeteren van de adaptatie aan de ziekte. De gezondheidstoestand verbeterde in geen van de drie klinische phenotypes binnen een jaar in de gebruikelijke zorg. Er werden daarentegen verschillen gevonden na klinische longrevalidatie tussen de drie klinische phenotypes. Alwaar de geadapteerde phenotypes significante verbetering lieten zien op vier tot zes subdomeinen van het NCSI, vonden we bij de niet geadapteerde patiënten een significante verbetering op tien van de elf subdomeinen van de gezondheidstoestand. Deze verbeteringen resulteerden in een betere balans tussen de vier domeinen, wat een betere adaptatie indiceert. Weten tot welk phenotype een patient behoort zal de behandelaar helpen bij de optimalisatie van de behandeling op maat.

Hoofdstuk 6

Het NCSI is ontwikkeld gebaseerd op data van patiënten met COPD. Aangezien het NCSI zowel generieke- als ziektespecifieke instrumenten voor het meten van de integrale gezondheidstoestand bevat, lijkt het aannemelijk dat het NCSI ook bij andere ziekten met longklachten gebruikt kan worden. De relevantie van het NCSI in een groep patiënten met ernstig astma hebben we geëvalueerd door deze te vergelijken met de internationaal meest gebruikte astma vragenlijsten; de Asthma Control Questionnaire (ACQ) en de Asthma Quality of Life Questionnaire (AQLQ). Op alle subdomeinen van het NCSI werden substantiële proporties van patiënten met ernstige problemen gevonden, wat suggereert dat alle subdomeinen relevant zijn in patiënten met astma. Op de subdomeinen subjectieve symptomen, moeheid, subjectieve beperkingen en algemene kwaliteit van leven werden de grootste proporties van patiënten met ernstige problemen geidentificeerd. Ook was er heterogeniteit in het aantal subdomeinen waarop patiënten ernstige problemen rapporteerden. De ACQ vertoonde conceptuele vergelijkbaarheid met twee van de acht subdomeinen van het NCSI, namelijk subjectieve symptomen en subjectieve beperkingen. De AQLQ vertoonde conceptuele vergelijkbaarheid met drie van de acht subdomeinen van het NCSI: subjectieve symptomen, subjectieve beperkingen en emoties bij benauwdheid. In tegenstelling tot de andere subschalen van de AQLQ meet de subschaal omgevingsstimuli een aspect van de integrale gezondheidstoestand dat niet gemeten wordt met het NCSI. Zowel de ACQ als de AQLQ meten beide geen kwaliteit van leven. Uit deze resultaten mag

geconcludeerd worden dat de NCSI meer subdomeinen van de integrale gezondheidstoestand meet die relevant zijn in patiënten met astma. Meer specifiek belangrijke aspecten zoals moeheid en algemene kwaliteit van leven worden niet gemeten met de ACQ en AQLQ.

Hoofdstuk 7

In 2007 vond een uitbraak van q-koorts plaats in Nederland. De beschreven studie in hoofdstuk 7 evalueert de integrale gezondheidstoestand van patiënten met q-koorts een jaar na de uitbraak en vergeleek deze resultaten met op leeftijd en geslacht gematchte controles die geen q-koorts hadden gehad. In beide groepen werden proporties van personen met normaal, verhoogd en ernstige problemen op alle subdomeinen van de NCSI gevonden. Maar patiënten met positieve q-koorts serologie rapporteerden meer problemen, een jaar na infectie, op de domeinen symptomen en functionele beperkingen in vergelijking met de controle groep. Met name moeheid was een prominent symptoom bij patiënten met q-koorts. Opvallend was dat de controle groep ook een lagere algemene kwaliteit van leven, gezondheidsgerelateerde kwaliteit van leven en hogere moeheidscores rapporteerden. Veel patiënten hadden een verslechterde integrale gezondheidstoestand een jaar na het doormaken van een q-koorts infectie. Het is belangrijk om de integrale gezondheidstoestand te monitoren in patiënten met q-koorts voor het bepalen van de nodige behandeling met als doel reductie of preventie van de consequenties op lange termijn.

Hoofdstuk 8

De verschillende studies in dit proefschrift werden bediscussieerd en nieuwe research vragen en klinische implicaties werden geformuleerd in dit hoofdstuk. Centraal in dit proefschrift stond de vraag waarom en hoe de integrale gezondheidstoestand zou gemeten moeten worden in de individuele patiënt. Een chronische ziekte heeft invloed op de hele persoon, niet alleen op het aangedane fysiologische systeem. Dit verantwoord het meten van meer dan alleen de fysiologische parameters. De studies lieten zien dat integrale gezondheidstoestand bestaat uit vele relatief onafhankelijke subdomeinen van fysiologisch functioneren, symptomen, functionele beperkingen en kwaliteit van leven, die allemaal gemeten moeten worden om een compleet beeld van de integrale gezondheidstoestand van de patiënt te krijgen. Dit is mogelijk met het NCSI. Alhoewel het NCSI ontwikkeld is voor patienten met COPD, is aangetoond dat het ook bruikbaar is bij patienten met andere chronische (long)ziekten. De presentatie van de resultaten van het NCSI op de PatientenProfielKaart maakt het makkelijker om de bevindingen te bespreken met de patiënt en helpt bij het op maat maken van de behandeling. Het is essentieel om te bepalen in welke mate de patiënt geadapteerd is aan zijn/haar ziekte, omdat aangetoond is dat dit een belangrijke determinant van de integrale gezondheidstoestand is.

LIST OF PUBLICATIONS

Published original articles

van Dam AS, van Loenhout JA, Peters JB, Rietveld A, Paget WJ, Akkermans RP, Olde Loohuis A, Hautvast JL, van der Velden J. A cross-sectional study to assess the long-term health status of patients with lower respiratory tract infections, including Q fever. Epidemiol Infect. 2014: 14:1-7.

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

Boer LM, Daudey L, Peters JB, Molema J, Prins JB, Vercoulen JH. Assessing the stages of the grieving process in chronic obstructive pulmonary disease (COPD): validation of the Acceptance of Disease and Impairments Questionnaire (ADIQ). Int J Behav Med. 2014: 21(3):561-70.

Sillen MJ, Vercoulen JH, van 't Hul AJ, Klijn PH, Wouters EF, van Ranst D, Peters JB, van Keimpema AR, Franssen FM, Otten HJ, Molema J, Jansen JJ, Spruit MA. Inaccuracy of estimating peak work rate from six-minute walk distance in patients with COPD. COPD. 2012: 9(3):281-8.

Tibosch MM, Sintnicolaas CJ, Peters JB, Merkus PJ, Yntema JB, Verhaak CM, Vercoulen JH. How about your peers? Cystic fibrosis questionnaire data from healthy children and adolescents. BMC Pediatr. 2011 Oct;11:86.

Morroy G, Peters JB, van Nieuwenhof M, Bor HH, Hautvast JL, van der Hoek W, Wijkmans CJ, Vercoulen JH. The health status of Q-fever patients after long-term follow-up. BMC Infect Dis. 2011: 11:97.

Peters JB, Heijdra YF, Daudey L, Boer LM, Molema J, Dekhuijzen PN, Schermer TR, Vercoulen JH. Course of normal and abnormal fatigue in patients with chronic obstructive pulmonary disease, and its relationship with domains of health status. Patient Educ Couns. 2011: 85(2):281-5.

Limonard GJ, Peters JB, Nabuurs-Franssen MH, Weers-Pothoff G, Besselink R, Groot CA, Dekhuijzen PN, Vercoulen JH. Detailed analysis of health status of Q fever patients 1 year after the first Dutch outbreak: a case-control study. QJM. 2010: 103(12):953-8.

Daudey L, Peters JB, Molema J, Dekhuijzen PN, Prins JB, Heijdra YF, Vercoulen JH. Health status in COPD cannot be measured by the St George's Respiratory Questionnaire alone: an evaluation of the underlying concepts of this questionnaire. Respir Res. 2010: 11:98.

Verhage TL, Vercoulen JH, van Helvoort HA, Peters JB, Molema J, Dekhuijzen PN, Heijdra YF. Maximal exercise capacity in chronic obstructive pulmonary disease: a limited indicator of the health status. Respiration. 2010;80(6):453-62.

Peters JB, Daudey L, Heijdra YF, Molema J, Dekhuijzen PN, Vercoulen JH. Development of a battery of instruments for detailed measurement of health status in patients with COPD in routine care: the Nijmegen Clinical Screening Instrument. Qual Life Res. 2009 Sep;18(7):901-12.

Vercoulen JH, Daudey L, Molema J, Vos PJ, Peters JB, Top M, Folgering H. An Integral assessment framework of health status in chronic obstructive pulmonary disease (COPD). Int J Behav Med. 2008;15(4):263-79.

Published letter

Sillen MJ, Vercoulen JH, van 't Hul AJ, Klijn PH, Wouters EF, van Ranst D, Peters JB, van Keimpema AR, Franssen FM, Otten HJ, Molema J, Jansen JJ, Spruit MA. The use of regression equations to estimate peak work rate in people with COPD -reply from the authors. COPD. 2013 Feb;10(1):120-121

Contributions to books

Vercoulen, JH, Peters JB, Molema J. Vermoeidheid bij Chronic Obstructive Pulmonary Disease (COPD). In: Handboek chronische vermoeidheid. Bleijenberg G, van der Horst H, van Houdenhove H, Knoop H, van der Meer J.

Published abstracts

Peters JB, Daudey L, Boer LM, Heijdra YF, Molema J, Vercoulen JH. Clinical phenotypes based on health status in COPD patients: differences in treatment response. Am J Respir Crit Care Med 185;2012:A6627

Peters J, Daudey L, Lahaije A, Boer L, de Geus E, Molema J, Heijdra Y, Vercoulen J. Screening of health status in patients with COPD in primary care is essential. Eur Resp J 2011; 38: Suppl. 55, 845s.

Boer L, Schermer T, Koopman A, Peters J, Heijdra Y, Vercoulen J, van der Heijden E. Effects of case management on hospitalisation and exacerbation rate in severe, complex COPD: A randomized controlled trial. Eur Resp J 2011; 38: Suppl. 55, 230s.

Sillen MJH, Vercoulen JH, van Het Hul AJ, Klijn PHC, Wouters EF, van Ranst D, Peters JB, van Keimpema ARJ, Franssen FME, Otten H, Molema J, Jansen JJ, Spruit MA. Estimation of peak work load based on 6-min walk distance and general demographics in patients with COPD: A new regression equation. Eur Resp J 2011; 38: Suppl. 55, 225s.

Sillen MJH, Vercoulen JH, van Het Hul AJ, Klijn PHC, Wouters EF, van Ranst D, Peters JB, van Keimpema ARJ, Franssen FME, Otten H, Molema J, Jansen JJ, Spruit MA. Validation of the current equations to estimate peak work load based on 6-min walk distance and general demographics in COPD patients entering pulmonary rehabilitation. Eur Resp J 2011; 38: Suppl. 55, 9s.

Peters JB, Boer LM, Daudey L, Molema J, Vercoulen JH. Different Patterns Of Daily Activity In Relation To Symptoms And Functional Impairment In COPD. Am J Respir Crit Care Med 181;2010:A4064

Daudey L, Boer LM, Molema J, Peters JB, Vercoulen JH. Activity Levels And Activity Patterns Need More Attention In The Treatment Of COPD. Am J Respir Crit Care Med 181;2010:A4063

Limonard G, Peters J, Nabuurs-Franssen M, Weers-Pothoff I, Besselink R, Dekhuijzen R, Vercoulen J, Groot K. Detailed analysis of health status of Q fever patients one year after the first Dutch outbreak: A case control study. Eur Resp J 2010; 36: Suppl. 54, 528s.

Peters JB, Boer LM, Daudey L, Molema J, Heijdra YF, Dekhuijzen PNR, Vercoulen JH. Limited clinical relevance of the 6MWD in relation to complaints and quality of life in COPD. Eur Resp J 2010; 34: Suppl. 53, 66s.

Peters JB, Daudey L, Boer LM, Molema J, Dekhuijzen PNR, Heijdra YF, Vercoulen JH. Relationship between mortality risk and health status in COPD. Eur Resp J 2010; 34: Suppl. 53, 67s.

Peters JB, Boer LM, Daudey L, Molema J, Heijdra YF, Dekhuijzen PNR, Vercoulen JH. Influence of pulmonary rehabilitation on 6mwd in relation to health status. Eur Resp J 2010; 34: Suppl. 53, 207s.

Sintnicolaas C, Vercoulen J, Peters J, Yntema J. Cystic fibrosis questionnaire reference data in a healthy, Dutch population 6-20 yrs. Eur Resp J 2010; 34: Suppl. 53, 61s.

Daudey L, van de Ven LH, Peters JB, Boer LM, Heijdra YF, Molema J, Dekhuijzen PNR, Vercoulen JH. Do COPD outpatients receive the care they need to improve their health status? Eur Resp J 2010; 34: Suppl. 53, 308s.

Boer LM, Daudey L, Peters JB, Bischoff EW, Molema J, Heijdra YF, Dekhuijzen PNR, Schermer TR, Vercoulen JH. The long-term impact of the grieving process on health status in COPD. Eur Resp J 2010; 34: Suppl. 53, 308s.

Peters JB, van de Ven LH, Heijdra YF, Molema J, Dekhuijzen PNR, Vercoulen JH. Powerful effects of multidisciplinary pulmonary rehabilitation on fatigue in COPD patients. Eur Resp J 2008; 30: Suppl. 51, 209s. (oral presentation)

Daudey L, Peters JB, Boer LM, Heijdra YF, Molema J, Dekhuijzen PNR, Vercoulen JH. Conceptual differences in health related quality of life (HrQoL) and quality of life (QoL) in COPD patients in relation to differences in natural course and determinants. Eur Resp J 2008; 30: Suppl. 51, 351s.

Boer LM, Daudey L, Peters JB, Heijdra YF, Molema J, Dekhuijzen PNR, Vercoulen JH. Assessing reluctance to adapt to COPD: preliminary results of the acceptance of disease and impairments questionnaire (ADIQ). Eur Resp J 2008; 30: Suppl. 51, 83s.

Daudey L, Heijdra YF, Peters JB, Boer L, Molema J, Dekhuijzen PNR, Vercoulen JH. Detailed description of Health Status (HS) in COPD outpatients. Am J Respir Crit Care Med 2008; 177; A827.

Daudey L, Peters JB, Heijdra YF, Molema J, Dekhuijzen PNR, Vercoulen JH. What sub domains of Health Status (HS) do the sections of St George's Respiratory Questionnaire (SGRQ) measure in COPD? Am J Respir Crit Care Med 2008; 177;A574.

Peters JB, Heijdra YF, Daudey L, Molema J, Dekhuijzen PNR, Vercoulen JH. Prevalence and severity of fatigue and its relationships with dyspnea and health status in COPD patients. Am J Respir Crit Care Med 2007;175;A642.

Vercoulen JH, Daudey L, Molema J, Vos P, Peters JB, Top M, Folgering H. An Integral Assessment Framework of Health Status in COPD. Am J Respir Crit Care Med 2007;175;A283.

DANKWOORD

Eindelijk is het zover: mijn proefschrift is af. Toen ik met het onderzoek begon had ik nooit verwacht dat zo lang zou kunnen duren. Het waren leuke jaren waarin ik veel geleerd heb niet alleen over onderzoek, maar ook over mezelf. Ik wil dan ook graag iedereen bedanken die hier een bijdrage in gehad heeft en/of mij op de een of andere manier heeft gesteund. Zonder iemand tekort te doen wil ik graag enkele personen persoonlijk bedanken.

Allereerst natuurlijk alle patiënten en gezonde proefpersonen die de tijd hebben genomen om alle testen en vragenlijsten te ondergaan. Zonder deze bijdrage had dit proefschrift nooit geschreven kunnen worden.

Graag wil ik mijn beide promotoren: Judith Prins en Richard Dekhuijzen, bedanken voor hun inzet en begeleiding bij het volbrengen van mijn proefschrift. Beste Judith, bedankt voor je betrokkenheid bij mijn promotie. Je duidelijke visie en vragen naar welke boodschap ik zelf zou willen overbrengen, hebben mij vooral bij de laatste loodjes van het proefschrift erg geholpen. Beste Richard, bedankt voor je altijd snelle en duidelijke feedback.
Mijn dank gaat tevens uit naar mijn copromotoren: Jan Vercoulen, Johan Molema en Yvonne Heijdra. Beste Jan, bedankt voor alle kansen en vrijheid die je mij de afgelopen jaren hebt geboden. Ik bewonder je gedrevenheid in het onderzoek en je vastbeslotenheid bepaalde dingen te veranderen. Naast geduldiger zijn, minder perfectionistisch (en nog een heel aantal dingen) heb ik veel van je geleerd en hoop ik de komende jaren nog meer te leren. Beste Johan, bedankt voor je eeuwige enthousiasme en dezelfde betrokkenheid bij de artikelen als die je voor patiënten had/hebt, zelfs nu je met pensioen bent. Zonder jou hadden de artikelen ook zeker niet zo'n mooie titels gehad. Beste Yvonne, bedankt voor je kritische inbreng en je eerlijke feedback op de artikelen. Ook de duidelijkheid waarmee je aangaf dat 'dokters dit niet snappen' heeft ervoor gezorgd dat we een betere aansluiting vonden in 'longenland'.
Beste professoren van de manuscriptcommissie: Prof. dr. W.J.J. Assendelft, Prof. dr. G.P. Westert en Prof. dr. R. Sanderman, bedankt voor het beoordelen van mijn manuscript.

Leonie, Tewe en Lonneke alle vier waren wij betrokken bij hetzelfde project. De wekelijkse overleggen waren misschien niet altijd even productief, maar zorgden wel voor de nodige energie om daarna weer hard aan de slag te gaan. Leonie, we hebben in die jaren veel met elkaar gedeeld van de eerste publicaties, congresbezoekjes tot aan de geboorte van de kinderen. Ik denk hier met plezier aan terug. Ik wens je heel veel succes met de GZ-opleiding en ben blij dat je nu op je plek zit. Tewe, ik heb er bewondering voor dat je naast je werk en opleiding je promotie hebt volbracht, het was een lange weg die je mooi hebt afgesloten. Ik vond en vind het nog steeds een hele eer dat ik jouw paranimf mocht zijn! Lonneke, bedankt voor je altijd luisterend oor en kritische meedenken bij het schrijven van de artikelen. Samen op een kamer was misschien soms wel te gezellig, maar zorgde zeker ook voor meer plezier in mijn werk. Al zit je nu wat verder weg ik hoop dat we nog veel met elkaar kunnen delen. Ik ben heel blij dat jij mijn paranimf wilt zijn!

Natuurlijk wil ik ook alle co-auteurs bedanken voor de vruchtbare samenwerking. Lous, bedankt voor de fijne samenwerking. Ik heb veel van je geleerd op het gebied van hoe dingen op te

schrijven zodat artsen het ook kunnen volgen. Iedere keer als ik weer te veel vanuit de psychologie schreef wees jij mij daar op. Daarnaast vond ik het ook erg fijn om de ervaringen m.b.t. het schrijfproces en alles wat daarbij komt met je te kunnen delen. Nog even en jouw proefschrift is ook af, ik ben erg benieuwd naar het eindresultaat. Gijs, bedankt dat jij als eerste in je onderzoek bij q-koorts patiënten het NCSI hebt gebruikt. Succes met de laatste loodjes van je promotie.

Collega's van de longrevalidatie en medische psychologie, jullie hebben er mede voor gezorgd dat ik altijd met plezier naar het werk ging. Bedankt voor jullie (blijvende) interesse voor de vorderingen van het proefschrift, jullie luisterend oor en hulp wanneer ik deze nodig had.
Mariska en Marlies, het ExcelEPD, EPIC en DBC/DOT hebben ervoor gezorgd dat ik regelmatig het onderzoek los kon laten. Jullie enthousiasme, het doorpakken en jullie kennis maken dat ik hoop de we in de komende jaren nog meerdere van deze projecten samen zullen aanpakken.
Stef, bedankt voor de vele avonduren waarin je de testorganizer/ Radquest hebt (door)ontwikkeld.

Dames van de Hennemanzaal: Anke, Laura, Marloes en Jorien, bedankt voor de al dan niet werkgerelateerde gesprekken en gezellige lunches, het is stil op de zolder zonder jullie.

Laura, Judith, Natasja, Alicia, Bram, Marleen, Elke, Joke en natuurlijk ook onze ex-stagiaires Evelien, Hanna, Neeliya & Samantha, bedankt voor de gezellige lunches, uitetentjes en gesprekken, dat er nog maar meer mogen volgen.

Lieve familie en vrienden, heel erg bedankt voor jullie steun de afgelopen jaren. Ook al was het voor jullie vaak de vraag waarom het allemaal zo lang duurde en wat ik dan überhaupt deed, toch bleven jullie geïnteresseerd en steunde jullie mij. Patrick en Patricia, Marcel en Penny, heel erg bedankt voor de gesprekken, leuke avonden, concertbezoeken, stapavonden, weekendjes weg, het samen sporten etc. deze hebben voor de nodige ontspanning gezorgd. Ik hoop dat er nog vele van deze avonden/dagen zullen volgen. Penny, ik ben heel erg blij dat jij mijn paranimf wilt zijn.

Pap, mam, John en Carry bedankt dat jullie er altijd voor mij (ons) zijn. Lieve papa en mama, jullie eeuwig vertrouwen dat het allemaal wel goed komt, ook al duurt het soms wel erg lang, het feit dat de kinderen altijd bij jullie terecht kunnen en we altijd aan kunnen schuiven voor een hapje hebben mij de rust gegeven om dit proefschrift te maken tot wat het nu is.
Tiny, Stefan, Lonneke, Sem en Liz, ik ben blij met jullie als schoonfamilie. Paul, jouw naam stond veel te vroeg in het boek, we zullen je niet vergeten.

'Last but not least' John, bedankt voor je liefde en steun tijdens deze lange weg. Ook al denk je soms anders over de dingen, toch laat jij mij altijd mijn eigen weg bewandelen. Ik ben je hier erg dankbaar voor en hoop dat we de komende 50 jaar net zo gelukkig zijn. Mathijs en Sven, jullie weten hoe belangrijk jullie voor mij zijn. Jullie mogen nooit vergeten dat ik erg trots op jullie ben!

-Jeannette-

Jeannette Jacobs-Peters werd op 23 september 1975 geboren in Boxmeer. In 1991 behaalde zij haar MAVO diploma aan de Meere te Boxmeer, waarna zij in 1993 haar HAVO diploma behaalde aan het Elzendaalcollege te Boxmeer. Na een studiejaar maatschappelijk werk en culturele maatschappelijke vorming te Arnhem met een propedeuse afgesloten te hebben startte zij in 1994 haar opleiding klinische psychologie aan de Katholieke Universiteit te Nijmegen, tegenwoordig Radboud Universiteit Nijmegen. In 2000 liep zij gedurende 9 maanden haar klinische stage op de longrevalidatie afdeling van Dekkerswald te Groesbeek. Alwaar zij in 2001 in de functie als psychologisch medewerker aan de slag ging. Na een studie onderbreking besloot zij in 2005 alsnog haar scriptie af te ronden en haar diploma in de klinische psychologie te behalen. In 2006 startte zij in de functie academisch klinisch medewerker waarin naast onderzoek een van de kerntaken is om de vertaling van wetenschappelijke uitkomsten naar de klinische praktijk te maken.
Jeannette Jacobs-Peters woont in Boxmeer en is getrouwd met John Jacobs. Zij hebben twee zonen Mathijs (geboren in 2002) en Sven (geboren in 2004).