Primary Care Respiratory Journal (2006) **15**, 84—91

PRIMARY CARE RESPIRATORY JOURNAL

ELSEVIER

http://intl.elsevierhealth.com/journals/pcrj/

ORIGINAL RESEARCH

COPD as a multicomponent disease: Inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care

Lotte M.G. Steuten [a,*], **Eva C. Creutzberg** [b,c], **Hubertus J.M. Vrijhoef** [a,d], **Emiel F. Wouters** [c]

[a] *Department of Health Care Studies, Faculty of Health Sciences, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands*
[b] *Centre for Integrated Rehabilitation and Organ Failure (CIRO), Horn; Clinical Research Unit, Horn, The Netherlands*
[c] *Department of Respiratory Medicine, University Hospital Maastricht, Maastricht, The Netherlands*
[d] *Department of Integrated Care, University Hospital Maastricht, Maastricht, The Netherlands*

Received 27 April 2005; accepted 15 September 2005

KEYWORDS
GOLD stages;
Dyspnoea;
BMI;
FFM depletion;
Primary care

Summary
Aims: To describe the distribution of COPD disease severity in primary care based on airway obstruction, and to assess the extent to which dyspnoea scores, body mass index (BMI) and fat free mass (FFM) index contribute to the distribution of COPD severity in primary care.
Design: Cross sectional population-based study.
Methods: 317 patients with COPD were recruited from an outpatient disease management programme. Prevalence of moderate to severe dyspnoea, underweight, obesity and FFM depletion by GOLD stage were measured.
Results: According to GOLD guidelines, 29% of patients had mild COPD, 48% moderate, 17% severe and 5% very severe. A substantial number of patients classified as GOLD stage 2 reported severe dyspnoea (28.1%) and/or suffered from FFM depletion (16.3%). Prevalence of low body weight strongly increased in GOLD stage 4. Prevalence of obesity is highest in GOLD stages 1 and 2.
Conclusion: The use of a multidimensional grading system, taking into account dyspnoea as well as the nutritional status of COPD patients, is likely to influence the distribution of disease severity in a primary care population. This might have

* Corresponding author. Tel.: +31 43 3881557; fax: +31 43 3884162.
E-mail address: L.Steuten@zw.unimaas.nl (L.M.G. Steuten).

1471-4418/$30.00
doi:10.1016/j.pcrj.2005.09.001

implications for prevention, non-medical treatment, and estimates of health care utilisation in primary care.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The most important cause of COPD is a long-term smoking history [1]. COPD causes considerable mortality and morbidity worldwide and is predicted to become the third most frequent cause of death and the fifth leading cause of disability by the year 2020 [2]. Moreover, the condition is often under-diagnosed and under-treated [3].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines established a definition as well as a classification system of airway obstruction [1]. The diagnosis of COPD is confirmed by a reduced forced expiratory volume in one second (FEV_1). There are then five stages of COPD, varying from stage 0 with patients being 'at risk', to stage 4 for patients with 'very severe COPD'. Although spirometric classification has proved to be useful in predicting health status [4], utilization of healthcare resources [5], development of exacerbations [6] and mortality in COPD, it is generally accepted that a single measurement of FEV_1 measurement incompletely represents the complex clinical consequences of COPD. Other risk factors such as the presence of hypoxemia or hypercapnia, a short distance walked in a fixed time, a high degree of functional breathlessness, as well as a low body mass and/or fat free mass (FFM) index, are associated with an increased risk of death [7–14].

As in other chronic inflammatory conditions, weight loss and tissue depletion are commonly seen in COPD patients [15]. The occurrence of tissue depletion varies from 20% in clinically stable outpatients up to 35% in patients who are eligible for pulmonary rehabilitation. In addition, the selective wasting of FFM despite relative preservation of fat mass, has been reported in COPD patients. Loss of FFM adversely affects respiratory and peripheral muscle function, exercise capacity and health status [16–20] and several studies using different COPD populations have convincingly shown that a low body mass index (BMI), low FFM, and weight loss are associated with an increased mortality risk [13,14,21]. Obesity, on the other hand, is strongly associated with an increase in dyspnoea, both in the general population as well as patients with COPD [22,23].

Dyspnoea represents the most disabling symptom of COPD and is a better predictor of the risk of death than is the FEV_1 [11]. Both the GOLD guidelines [1] and the American Thoracic Society (ATS) [24] recommend that a patient's perception of dyspnoea should be included in any new staging system for COPD. The degree of dyspnoea can be measured with the MRC dyspnoea scale [25], which correlates with other dyspnoea scales and scores of health status [26,27]. Moreover, it is simple to administer and therefore feasible to apply in a primary care setting.

Given the above, and in accordance with the BODE-study [7], it is desirable to pay attention to respiratory, perceptive and systemic aspects in order to produce a composite picture of disease severity of COPD. The BODE-study, however, was performed in a secondary care setting with a group of elderly patients, most of them suffering from severe COPD [7]. This population is not representative of a primary care population. Moreover, despite data describing the prevalence of COPD, the distribution of disease severity in the primary care population is mainly unknown [28].

Therefore, the aims of this study were: (1) to describe the distribution of COPD disease severity in primary care based on airway obstruction; and (2) to assess the extent to which dyspnoea scores, BMI and FFM index contribute to the distribution of COPD severity in primary care. In addition, we investigated any differences between the proportion of males and females within each GOLD stage suffering from severe dyspnoea, underweight, obesity or depleted FFM. The potential impact of exercise capacity on disease severity in a primary care population was not studied, since it is not feasible to perform routinely the six-minute walking test in this setting, given the number of patients, the lack of machinery in the GPs' offices, and the limited time for consultation.

Methods

Patients were recruited between May 2002 and March 2003 from an outpatient disease management program that was implemented in the Maastricht region of the Netherlands (NL). Twenty general practitioners (GPs) from 16 general practices participated in the programme. Inclusion criteria were: diagnosis of COPD, based on spirometry; and age $\geq$18 years. Exclusion criteria were: serious co-morbidity such as lung cancer or congestive heart failure. Following a well-defined procedure, respiratory nurse specialists evaluated respiratory symptoms and lung function of patients submitted by the GPs. This procedure took place in the primary care setting. Diagnosis and definition of COPD severity was established in accordance with the GOLD guidelines by the core team consisting of a pulmonologist, a GP and a nurse specialist. GOLD stage 0 (at risk) is diagnosed when patients report chronic cough and sputum production whilst their lung function is still normal. GOLD stage 1 (mild COPD) is defined as a ratio of FEV_1/forced vital capacity (FVC) <70% but with the $FEV_1 \geq 80\%$ predicted. GOLD stage 2 (moderate COPD) is diagnosed if the FEV_1 is between 50% and 80% predicted. Gold stage 3 (severe COPD) is defined as an FEV_1 between 30% and 50% predicted, and GOLD stage 4 (very severe COPD) is diagnosed if FEV_1 is less than 30% predicted. Patients with a confirmed diagnosis of COPD were included in the study. Written informed consent was obtained from each patient.

Lung function measurements

Post-bronchodilator FEV_1 was measured according to the ATS criteria before and after administration of a bronchodilator (salbutamol, 400 μg) using a hand held spirometer (Vitalograph; Vitalograph Ltd, Buckingham, United Kingdom). Patients were instructed not to use bronchodilators on the day of pulmonary function assessment or at least not within six hours before measurement. Nurse specialists were specially trained to perform the pulmonary function measurements. Spirometers were calibrated daily. All patients were studied in a sitting position. Data from the flow-volume curve with the highest sum of FVC and FEV_1 were used for calculations. FEV_1 was expressed as FEV_1% predicted, based on gender, height, and age, using the reference values of the European Respiratory Society [29].

Dyspnoea measurement

The Medical Research Council (MRC) scale was used for grading the effect of breathlessness on daily activities. The scale measures perceived respiratory disability by allowing patients to indicate the extent to which their breathlessness affects their mobility. Disability was defined according to the WHO definition of disability, being 'any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being' [25]. The MRC dyspnoea scale consists of five statements being: 1 = 'I only get breathless with strenuous exercise'; 2 = 'I get short of breath when hurrying on the level or up a slight hill'; 3 = 'I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level'; 4 = 'I stop for breath after walking 100 meters or after a few minutes on the level'; 5 = 'I am too breathless to leave the house'. Patients select the grade that applies to them. Patients are considered moderately or seriously disabled due to breathlessness if their MRC score is $\geq$3 since this is associated with worsening of exercise tolerance, health status and mood state [25].

Anthropometrical measurements

Measurement of height was made by clinical stadiometer in bare or stocking feet. Body weight was measured with a calibrated precision scale with subjects wearing their normal clothes but without shoes. To correct for this, 1 kg of the measured body weight was subtracted for each person. BMI, defined as weight (kilograms) divided by the square of height (meters), was calculated. Patients were considered underweight if their BMI was $\leq$21 kg/m^2, and obese if their BMI was >30 kg/m^2 [1].

Measuring fat free mass

FFM was measured by means of whole body bioelectrical impedance analysis with the Bodystat 1500 (Bodystat Ltd; Isle of Man, British Isles). Injector electrodes are placed on the dorsal surfaces of the foot and wrist, and detector electrodes are placed between the radius and ulna (styloid process) and at the ankle (between the medial and lateral malleoli). The FFM-index (FFMI) was calculated from height^2/resistance and body weight using a regression formula corrected for COPD. Patients were considered as having a depleted FFM if FFMI $\leq$15 kg/m^2(women) or $\leq$16 kg/m^2 (men) [30].

Statistical considerations

Patients were classified by means of lung function (GOLD stage), MRC score, BMI and FFMI. Descriptive statistics were applied in order to identify the prevalence of GOLD stages in a primary care population. Also, the numbers of patients classified in GOLD stages 0, 1 or 2, whilst having an MRC score ≥3, or a BMI either ≤21 kg/m^2 or >30 kg/m^2, or a FFMI ≤15 kg/m^2 (women) or ≤16 kg/m^2 (men), were computed. Differences in baseline characteristics between GOLD stages were assessed for statistical significance at $\alpha = 0.05$ using independent-samples *t*-tests for normally distributed data and Mann-Whitney-U-tests for the variables sex and smoking. Potential differences between the proportion of males and females suffering from severe dyspnoea, underweight, obesity or depleted FFM within each GOLD stage were analysed with Chi-square tests at a 5% uncertainty level. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, U.S.A.). All data are presented as means (±sd) unless stated otherwise.

Results

Of the 355 eligible patients, 317 (89.3%) participated. Baseline characteristics of the 317 subjects with a diagnosis of COPD are shown in Table 1. Twenty-nine percent of the COPD patients were classified as having mild COPD, 48% as moderate, 17% as severe and 5% as very severe. The relative number of females decreased with increasing severity of the disease. The percentage of smokers was highest in the GOLD 2 group (48.3%), while the average number of pack years smoked was highest in GOLD 3 (40.2 ± 25.1 yrs). The average number of pack years differed between men (32.6 ± 21.8) and women (27.3 ± 15.2), this difference being statistically significant ($p = .034$) (Students *t*-test, two-sided with $\alpha = .05$).

Table 2 shows the percentage of patients having an MRC score ≥3, a BMI ≤21 kg/m^2 or >30 kg/m^2, or a FFMI ≤15 kg/m^2 (women) or ≤16 kg/m^2 (men), by GOLD stage. A substantial proportion of GOLD 2 patients reported severe dyspnoea (28.1%) and/or suffered from FFM depletion (16.3%). The prevalence of low body weight increased by 10% over GOLD stages 1 to 3, but strongly increased in GOLD stage 4. The prevalence of obesity was highest in GOLD stages 1 and 2.

Significant sex differences were found with regard to FFM-depletion in GOLD stage 2 ($p = 0.002$) and severe dyspnoea in GOLD stage 3 ($p = 0.021$).

Discussion

In this study the distribution of COPD severity in an outpatient population has been assessed according to the GOLD classification system [1]. Moreover, the proportion of patients with mild to moderate COPD (GOLD stage 1 and 2) suffering from severe dyspnoea, underweight, obesity or FFM-depletion was investigated. Also, gender prevalence differences with regard to these measures have been studied.

In terms of our first research question on the distribution of COPD disease severity, 77.8% of patients had mild or moderate COPD, and 22.2% had severe or very severe disease as defined by GOLD criteria. The distribution of disease severity in primary care in this study compares well with other studies performed in The Netherlands and the UK. The relatively small number of females in GOLD stages 2, 3 and 4 might be explained by lower prevalence rates of COPD for women as previously reported by Feenstra et al. [31]. Also, it may be

Table 1 Baseline characteristics categorized by GOLD stage.

	GOLD ($n = 317$)			
	1	2	3	4
N (%)	93 (29.4)	153 (48.3)	54 (17.0)	17 (5.3)
M/F	45/48	84/69	35/19	14/3
Age	56.6 (±14.4)	61.8 (±13.7)*	65.7 (±11.8)	68.8 (±11.5)
FEV1% pred	91.8 (±10.0)	64.7 (±8.3)*	42.3 (±4.9)*	25.1 (±4.8)*
FVC	118.2 (±15.9)	94.4 (±18.6)*	75.3 (±17.9)*	72 (±23.6)
FEV1/FVC	0.63 (±0.1)	0.56 (±0.1)*	0.47 (±0.1)*	0.34 (±0.1)*
MRC	1.6 (±0.85)	2.2 (±1.03)*	2.8 (±1.12)*	3.6 (±1.11)*
BMI	26.5 (±4.13)	26.7 (±5.48)	25.7 (±4.53)	22.0 (±5.31)*
FFMI	17.8 (±2.4)	17.8 (±2.5)	17.6 (±2.3)	16.1 (±2.5)
% smokers	43.5	48.3	31.5*	23.5
Pack years	23.1 (±15.6)	31.5 (±18.1)*	40.2 (±25.1)*	27.1 (±15.3)

* Indicates statistical significant difference between this GOLD stage and the preceding one, tested with an independent-samples *t*-test or a Mann-Whitney-U test when appropriate ($\alpha = 0.05$).

Table 2 Prevalence of severe dyspnoea, underweight, obesity and muscle wasting by GOLD stage.

% (no.) of patients	GOLD 1			GOLD 2			GOLD 3			GOLD 4		
	overall	males	females	*overall*	males	females	*overall*	males	females	*overall*	males	females
MRC ≥3	*9.7 (9)*	6.6 (3)	12.5 (6)	*28.1 (43)*	31.0 (26)	24.6 (17)	*53.7 (29)*	34.3 (12)*	89.5 (17)*	*82.4 (14)*	85.7 (12)	66.7 (2)
BMI ≤21	*6.5 (6)*	6.6 (3)	6.3 (3)	*10.5 (16)*	7.1 (6)	14.5 (10)	*16.7 (9)*	20.0 (7)	10.5 (2)	*47.1 (8)*	42.9 (6)	66.7 (2)
BMI >30	*16.1 (15)*	15.6 (7)	16.7 (8)	*23.5 (36)*	25.0 (21)	21.7 (15)	*9.3 (5)*	11.4 (4)	5.3 (1)	*5.9 (1)*	0.0 (0)	33.3 (1)
FFM ≤15♀ or ≤16♂	*11.8 (11)*	8.8 (4)	14.6 (7)	*16.3 (25)*	7.1 (6)*	27.5 (19)*	*11.1 (6)*	14.3 (5)	5.3 (1)	*52.9 (9)*	50.0 (7)	66.7 (2)

* Indicates statistically significant difference between males and females tested with Chi-square test at $\alpha = 0.05$.

influenced by the lower number of smoking pack years in women, as found in this study, or gender differences in occupational exposures [32,33].

With respect to our second objective, we found that a substantial proportion of primary care patients with mild to moderate COPD reported moderate to severe dyspnoea (mild 9.7%; moderate 28.1%) and/or serious muscle wasting (mild 11.8%; moderate 16.3%). Prevalence of low body weight only strongly increased in patients with very severe COPD while prevalence of obesity was highest among patients with mild to moderate COPD. Gender differences were found with regard to depleted FFM in GOLD stage 2 and severe dyspnoea in stage 3. It needs to be stressed that the prevalence of FFM depletion within an outpatient population is normally found to be around 25%, independently from disease severity, as compared to the prevalence of 11.8% to 16.3% that we found in this study. Consequently, our data seem to be underestimating the potential impact of FFM-depletion on distribution of disease severity in primary care, rather than overestimating.

The study results suggest that the use of a multidimensional grading system which takes the nutritional status of COPD patients into account as well as dyspnoea, is likely to influence the distribution of COPD severity in a primary care population. However, the exact impact of using such a multidimensional system instead of the GOLD criteria is hard to assess because not all necessary data are available in primary care. For example, the multidimensional grading system as proposed by Celli et al. seems difficult to apply in primary care since data on exercise capacity are generally not available here. Data on FFM, however, are more commonly available *and* they have been shown to be strongly related to exercise capacity [16,34]. Measures of BMI on the other hand were found to be of relatively less importance in determining disease severity, as has also been reflected in the BODE-index where relatively little weight was attached to changes in BMI [7]. Therefore, more emphasis might be placed on assessing body composition in primary care, and it seems worthwhile to include this measure in a multidimensional grading system.

A shift in severity distribution might have implications for prevention, non-medical treatment, and estimates of health care utilisation. Firstly, since the majority of patients in primary care suffer from mild to moderate COPD, they are at risk of deterioration in their disease with increasing age. Also, many of these patients are still current smokers, with smoking prevalence rates of 43.5% in mild COPD and 48.3% in moderate disease. Since smoking cessation reduces the subsequent rate of lung function decline in patients with mild to moderate airflow limitation [35], the chief benefits of smoking cessation are to be expected in these patient groups. A combined strategy of nicotine-replacement therapy with counselling or antidepressants (bupropion or nortryptiline) with counselling, in which the physiological as well as the psychological aspects of smoking cessation are treated, seems to be most effective [36].

Secondly, a substantial proportion of patients classified in GOLD stage 1 or 2 already show symptoms of moderate to severe disability due to dyspnoea and/or serious muscle wasting. Previous studies have suggested that any given FEV_1 may be associated with a wide range of disability [25] and therefore that direct measurements of disability are clearly complimentary in assessing the severity of disease. Moreover, dyspnoea is a better predictor of the risk of death than is the FEV_1 [11].

Thirdly, both retrospective and prospective studies within several COPD populations provide evidence for a relationship between low BMI and higher mortality rates [12,13] with relative risks ranging from 1.42 in women to 1.64 in men [13]. Furthermore, it has been reported that underweight patients are more dyspnoeic than normal weight patients, partly as a consequence of decreased respiratory muscle strength [37]. The functional consequences of being underweight but also of having FFM depletion have been reflected in a decreased health status as measured by the St. George's Respiratory Questionnaire (SGRQ) [38] and decreased physical functioning. Depletion of FFM caused greater impairment in the activity and impact scores of the SGRQ than weight loss [20]. The specific relationship between FFM and mortality was first reported by Marquis et al. [39], demonstrating that a small midthigh muscle cross-sectional area and FEV_1 were found to be the only significant predictors of mortality in patients with stable COPD (mean FEV_1 $42 \pm 16\%$ predicted). Recently, Schols et al. have shown that FFM (relative risk: 0.90; 95% CI: 0.48, 0.96; $p = 0.003$) is an independent predictor of mortality [14].

Several studies have shown that restoration of the distorted energy balance by nutritional support, in combination with training or revalidation, results in a significant increase in body weight, fat-free mass, respiratory muscle function and even in the immune response [12,40—44]. Nevertheless, nutritional support for severely underweight COPD patients may only have limited effect on the recovery of functional exercise abilities, because compliance appears to be difficult [45]. For the obese patients in these GOLD stages, nutritional advice is also worthwhile since obesity is associated with dyspnoea [22,23].

Overall, the results of this study imply that awareness of dyspnoea and of the nutritional aspects of COPD is necessary in order to avoid underscoring COPD disease severity in primary care. This should be accomplished by integrating simple measurements of dyspnoea and nutritional status within classification systems for disease severity. Subsequently, targeted interventions such as smoking cessation, exercise training and nutritional interventions can be used as a means of secondary prevention [12]. Furthermore, these findings have implications for the estimation of the future burden of COPD in terms of health care utilisation [3,46]. Since health care utilisation is commonly matched to stages of disease severity (commonly the GOLD stages), the estimated amount of health care utilisation within a specific disease stage and within a specific time lag needs to be recalculated when the distribution of patients over these disease severity stages changes. Not only patient numbers per severity stage will change, but from previous studies it is also known that low BMI as well as depleted FFM are related to higher utilisation of, for example, in-patient services [46]. The relationship between MRC score and health care utilisation needs to be investigated more extensively for this purpose. In addition, mortality rates per severity stage need to be adjusted because of the impact that dyspnoea, BMI and FFM have on mortality rates.

Conflict of interest

None declared.

References

[1] Pauwels RA, Buist S, Calverly PMA, Jenkins CR, Hurd SS. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. Am J Respir Crit Care Med 2001;163:1256—76.

[2] Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990—2020: Global Burden of Disease Study. The Lancet 1997;349:1436—42.

[3] Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. Respir Med 2003;97:S3—14.

[4] Ferrer M, Alonso J, Morera J, et al. Chronic obstructive pulmonary disease stage and health-related quality of life. Ann Int Med 1997;127:1072—9.

[5] Friedman M, Serby C, Menjoge S, Wilson J, Hileman D, Witek T. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 1999;115:635—41.

[6] Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297—303.
[7] Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. NEJM 2004;350(10):1005—12.
[8] Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal therapy in hypoxemic chronic obstructive pulmonary disease: a clinical trial. Ann Intern Med 1980;93:391—8.
[9] The Intermittent Positive Pressure Breathing Trial Group. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease: a clinical trial. Ann Intern Med 1983;99:612—20.
[10] Gerardi DA, Lovett L, Benoit-Connors ML, Reardon JZ, ZuWallack RL. Variables related to increased mortality following outpatient pulmonary rehabilitation. Eur Respir J 1996;9:431—5.
[11] Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnoea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121:1434—40.
[12] Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1791—7.
[13] Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:1856—61.
[14] Schols AMWJ, Broekhuizen R, Weling-Scheepers CA, Wouters EFM. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 2005;82:53—9.
[15] Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. Chest 2002;121:127S—30S.
[16] Baarends EM, Schols AM, Mostert R, Wouters EF. Peak exercise response in relation to tissue depletion in patients with chronic obstructive pulmonary disease. Eur Respir J 1997;10:2807—13.
[17] Palange P, Forte S, Felli A, Galassetti P, Serra P, Carlone S. Nutritional state and exercise tolerance in patients with COPD. Chest 1995;107:1206—12.
[18] Engelen MP, Schols AM, Does JD, Wouters EF. Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 2000;71:733—8.
[19] Palange P, Forte S, Onorati P, et al. Effect of reduced body weight on muscle aerobic capacity in patients with COPD. Chest 1998;114:12—8.
[20] Mostert R, Goris A, Weling-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. Respir Med 2000;94:859—67.
[21] Schols AM. Nutrition in chronic obstructive pulmonary disease. Curr Opin Pulm Med 2000;6:110—5.
[22] Berner YN. The contribution of obesity to dyspnoea in elderly people. Age Ageing 2001;30(6):530.
[23] Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, Burr ML. Dyspnoea and quality of life in older people at home. Age and Ageing 2001;30:155—9.
[24] Definitions, epidemiology, pathophysiology, diagnosis, and staging. Am J Resp Crit Care Med 1995;152(Suppl): S78—83.
[25] Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the MRC dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581—6.
[26] Mahler DA, Einberg DH, Wells CK, Feinstein AR. The measurement of dyspnea: contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;85:751—8.
[27] 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. Am J Respir Crit Care Med 1998;157: 785—90.
[28] Hoogendoorn M, Rutten-van Mölken MPMH, Hoogenveen RT, et al. A dynamic population model of disease progression in COPD. Eur Respir J 2005;26:223—33.
[29] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working party Standardization of Lung Function Tests, European Community for Steel and Coal; Official Statement for the European Respiratory Society. Eur Respir J 1993;6:5—40.
[30] Creutzberg EC, Wouters EF, Mostert R, Weling-Scheepers CA, Schols AM. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. Nutrition 2003;19: 120—7.
[31] Feenstra TL, Van Genugten MLL, Hoogenveen RT, Wouters EF, Rutten-van Mölken MPMH. The impact of aging and smoking on the future burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164:590—6.
[32] Varkey AB. Chronic obstructive pulmonary disease in women: exploring gender differences. Curr Opin Pulm Med 2004;10:98—103.
[33] Le Moual N, Kennedy SM, Kauffman F. Occupational exposures and asthma in 14,000 adults from the general population. Am J Epidemiol 2004;160:1108—16.
[34] Franssen FME, Broekhuizen R, Janssen PP, Wouters EFM, Schols AMWJ. Effects of whole-body exercise training on body composition and functional capacity in normal-weight patienst with COPD. Chest 2004;125:2021—8.
[35] Anthonisen NR. Smoking, lung function, and mortality. Thorax 2000;55:729—34.
[36] Wagena EJ, Huibers MJ, Van Schaijk CP. Therapies for smoking cessation (antidepressants, nicotine replacement and counselling) and implications for the treatment of patients with chronic obstructive pulmonary disease. Ned Tijdsch Geneeskd 2001;145(31):1492—6 (*in Dutch*).
[37] Sahebjami H, Sathianpitayakul E. Influence of body weight in emphysema. Am J Respir Crit Care Med 2000;161: 886—90.
[38] Shoup R, Dalsky G, Warner S, et al. Body composition and health-related quality of life in patients with obstructive airways disease. Eur Respir J 1997;10:1576—80.
[39] Marquis K, Debigaré R, Lacasse Y, et al. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002;166:809—13.
[40] Efthimiou J, Fleming J, Gomez C, Spiro SG. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;137:1075—82.
[41] Whittaker JS, Ryan CF, Buckley PA, Road JD. The effects of refeeding on peripheral and respiratory muscle function

in malnourished chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1990;142:283—8.
[42] Rogers RM, Donahoe M, Costantino J. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;146:1511—7.
[43] Schols AMWJ, Soeters PB, Mostert RM, Pluymers RJ, Frantzen PJ, Wouters EFM. Physiological effects of nutritional support and anabolic steroids in COPD patients. Am J Respir Crit Care Med 1995;152:1268—74.
[44] Fuenzalida CHE, Petty TL, Jones PLM, Hambridge HM. The immune response to short-term nutritional intervention in advanced chronic obstructive pulmonary disease. Am Rev Respir Dis 1990;142:49—56.
[45] Ferreira IMB, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. Chest 2000;117:672—8.
[46] Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J 1997;10:417—23.

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Available online at http://www.thepcrj.com