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Determinants and impact of fatigue in patients with chronic obstructive pulmonary disease☆

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KEYWORDS
Fatigue;
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Summary
Rationale: The perception of fatigue in COPD has been associated with reduced health status. We have shown that exacerbations are associated with reduced activity and health status. However, the relationship between fatigue and exacerbation is unknown.
Objectives: To investigate the hypothesis that increased fatigue is related to physical inactivity and COPD exacerbations.
Methods: Fatigue was studied in COPD and age-matched control subjects. The relationship between fatigue and stable patient characteristics in COPD, and the effect of exacerbation on fatigue were evaluated.
Measurements: 107 COPD patients mean age 69 years (range 43–86), FEV_1 53% (SD 21), and 30 aged-matched control subjects; Functional Assessment of Chronic Illness Therapy-Fatigue Scale, Centre for Epidemiological Studies Depression Scale.
Main results: Fatigue in COPD patients was significantly increased compared to control subjects (mean 35.3 units (SD 11.0) versus 43.2 (10.5), $p = 0.001$). Increase in fatigue in COPD was related to reduced time spent outdoors ($r = -0.43$, $p < 0.001$), increase in depression ($r = -0.59$, $p < 0.001$) and annual exacerbation frequency ($r = -0.27$, $p = 0.005$).

Fatigue increased at exacerbation in 31/32 patients. Overall, fatigue increased by 8.3 units (5.9), $p < 0.001$. Change in fatigue at exacerbation was related to increase in depression ($r = -0.46$, $p = 0.008$). Fatigue recovered at 6 weeks following exacerbation.
Conclusions: The perception of fatigue increased in patients with COPD compared to age-matched control subjects, and associated with morbidity when patients were stable and at exacerbation.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow obstruction which is mainly irreversible.[1] It is associated with significant comorbidities,[2] and extrapulmonary manifestations. Fatigue, the perception of mental or physical exhaustion due to exertion, may be a common symptom in COPD,[3,4] and it has been associated with reduced health status, dyspnoea [5,6] and depression.[6]

COPD exacerbations are episodes of sustained deterioration in respiratory symptoms associated with increased systemic inflammation,[7] muscle weakness,[8] reduced lung function,[9] daily activity[10,11] and health status.[12] Exacerbations are responsible for 10% of emergency medical admissions in the U.K,[13] and associated with a significant economic health-burden.[14] Despite this, it is not known whether fatigue increases at exacerbation and thus could contribute to the morbidity of exacerbations including depressive symptoms, or whether patients with more frequent exacerbations have increased fatigue.

There is evidence to suggest that reduced physical activity in COPD[15] may lead to myopathy and weakness,[16] associated with increased healthcare utilization[11,17] and poor prognosis.[18] In contrast, exercise training as part of pulmonary rehabilitation has been shown to improve the perception of fatigue,[19] functional exercise capacity[19–21] and health status.[19,20] However, the relationship between the perception of fatigue and daily outdoor physical activity[10] has not been previously described.

This study investigated for the first time the relationship between fatigue and exacerbations, fatigue and depression at exacerbation, and the perception of fatigue and time spent outdoors, an indicator of physical activity. Some of the results of this study have been previously reported in the form of abstracts.[22–24]

Methods

Recruitment of COPD patients and control subjects

107 patients with COPD and 30 control subjects were recruited between April 2006 and November 2007 from the London COPD cohort. This is a rolling cohort of COPD patients and control subjects recruited from the community and respiratory clinics to prospectively investigate the mechanisms of COPD exacerbation.[7,9,10,12] COPD was defined as a post-bronchodilator forced expiratory volume in 1 s to forced vital capacity ratio (FEV_1/FVC) of less than 70%, and features consistent with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[25] for the diagnosis of COPD.

Control subjects had no previous history of COPD, with an FEV_1/FVC of more than 70%. All COPD patients and control subjects with a history of malignant disease, immunodeficiency, significant inflammatory or other respiratory disease were excluded.

At recruitment COPD patients were in a stable condition, at least four weeks from their last exacerbation. The average daily time outdoors, over a period of 6 months before and after assessment, was calculated for 86 COPD patients with completed diary cards. All COPD patients and control subjects were assessed with the MRC Dyspnoea scale[26] and a 10 cm Visual Analogue Scale at rest, (VAS,[27]). Smoking status, smoking pack years and history of comorbidity was noted. Patient questionnaires (detailed below) were also completed for assessment of fatigue using the validated Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue,[28–30]), depression (with Centre for Epidemiologic Studies Depression Scale, CES-D,[31–33]), and quality of life (with St. George's Respiratory Questionnaire, SGRQ,[34]). Height and weight were measured, in addition to baseline pulse oximetry (digital Minolta Pulsox TS-7, Japan), and lung function using a volumetric storage spirometer (Vitalograph 2160, Buckingham, England). For patients with obstructive spirometry, an assessment of reversibility to B_2-agonist was made, after inhalation of 400 mcg salbutamol from a metered-dose inhaler via spacer.

All COPD patients were phenotyped by providing a 7 ml sample of blood for measurement of haemoglobin (Hb, Advia 2120 Haematology System, Siemens Medical Solutions Diagnostics, New York, U.S.) and serum C-reactive protein (CRP, using an Olympus luminometric analyzer (Olympus Life and Material Science Europa GmbH, Hamburg, Germany) within 2 h. The limit of detection for serum CRP was 0.3 mgl^{-1}.

This study was approved by the Royal Free Hospital Research Ethics Committee and all patients gave written informed consent. Some of the depression scores in COPD patients have been reported in a study of COPD and depression,[35] but the data of fatigue which is the main focus of this paper has not been previously published.

Self-complete questionnaires

The FACIT-Fatigue is a simple 13 point questionnaire which provides a validated measure of the level of fatigue in chronic disease[28,29] and relates to performance status. The response to each question is measured on a scale of 0–4, and scored such that the minimum overall score of 0 reflects the highest level of fatigue measurable and the maximal score of 52 reflects the lowest possible level of fatigue.[30] This paper refers to fatigue as a symptom from here onwards, but it should be noted that with this questionnaire, a higher FACIT-Fatigue score indicates less fatigue.

The CES-D is a 20 point questionnaire which assesses the prevalence of depression and magnitude of change and associated symptoms in COPD[31] and the general population.[32] This depression questionnaire excludes somatic symptoms such as fatigue. Only completed questionnaires were used to calculate a CES-D score which has a maximum attainable score of 60. A score of 16 or higher is consistent with clinical depression, according to validation studies comparing it to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for clinical depression.[33]

The SGRQ[34] measures health impairment in patients with respiratory disease and has three component scores which provide a measure of the effects of disease on the domains of symptoms, activity and impact.

COPD exacerbation and follow-up

COPD patients in the London COPD cohort were trained to complete daily diary cards of time spent outdoors and any increase in respiratory symptoms. All patients with COPD were routinely seen three monthly in clinic, where diary cards were reviewed and spirometry was recorded. Patients were asked to contact our study team when experiencing increase in daily symptoms and usually seen within 48 h for assessment of symptoms and confirmation of exacerbation according to the definition described later. Some patients did not report their exacerbations at onset and therefore fatigue was measured at a median of 4.3 days. Data collected after 14 days after the onset of an exacerbation was excluded. All patients were assessed prior to initiation of therapy for exacerbation with follow-up arrangement for 6 weeks from an exacerbation onset.

Definition of exacerbation

Exacerbations were identified using patient diary cards, by our previously validated criteria[7,9,10,12] of two consecutive days of two symptoms or more with at least one major symptom, or if in the opinion of the attending clinician the patient was exacerbating. Major symptoms were an increase in dyspnoea, sputum volume or purulence and minor symptoms were increase in cough, wheeze, sore throat or symptoms of a cold (increase in nasal congestion or discharge).

Exacerbation frequency

The annual exacerbation incidence was determined from diary cards in the year prior to recruitment for 96 patients.[12] In 11 patients who withdrew within one year, the self-reported exacerbation history was used. The median annual exacerbation incidence was 2 per year (interquartile range, IQR 0—3). 55 patients with 2 or more exacerbations per year were defined as frequent exacerbators and the remaining 52 patients as infrequent exacerbators.

Statistical analysis

The data was analysed using SPSS version 11 (SPSS Inc, Chicago, U.S.). Parameters were tested for normality using the Kolmogrov—Smirnov test. Normally distributed data were expressed as mean and standard deviation (SD), and skewed data as median and interquartile range (IQR). Correlations were assessed by Pearson or Spearman's rank correlation as appropriate. Differences in fatigue between patients grouped according to categorical parameters such as MRC Dyspnoea scale or GOLD staging were assessed by a one-way ANOVA. An unpaired *t*-test was used to test the effect of co-morbidity on fatigue. Mutiple regression analysis was used to ascertain the relative contribution of factors related to fatigue. A single fatigue measurement when the patient was stable and the first reported exacerbation were selected to avoid bias and to simplify analysis. Paired *t*-test analyses were used to evaluate fatigue in the stable state compared to exacerbation, and at 6 weeks

Table 1 Stable characteristics of 107 stable COPD patients and 32 patients subsequently seen at exacerbation.

	107 stable COPD patients		Stable data for subgroup of 32 patients seen at an exacerbation		Stable data for subgroup of 75 patients not seen at an exacerbation		Comparison of stable characteristics between 2 subgroups
	Mean	SD	Mean	SD	Mean	SD	*p* value
Age (years)	69.4	8.2	65.9	9.2	70.9	7.3	0.004
FEV_1 (litres)	1.3	0.6	1.3	0.6	1.3	0.6	0.71
FEV_1(% predicted)	53.1	21.1	51.5	20.7	54.0	21.6	0.54
FVC (litres)	2.8	1.0	2.7	0.9	2.8	1.0	0.59
BMI (kgm^{-2})	25.9	5.4	26.4	4.5	25.7	5.7	0.58
FACIT-Fatigue Scale	35.3	11.0	33.7	9.6	36.0	11.6	0.34
CES-D scale	14.0	11.2	13.0	9.9	14.5	11.7	0.55
VAS (0—10 cm)	4.4	2.3	4.9	2.0	4.2	2.4	0.13
TOTAL SGRQ score	49.2	18.0	54.0	16.4	47.2	18.3	0.07
Activity domain	65.2	23.0	67.2	19.8	64.3	24.3	0.55
Impact domain	36.1	19.3	41.3	18.6	33.9	19.4	0.07
Symptom domain	62.3	20.0	70.7	17.7	58.7	20.0	0.004
Haemoglobin (g/dl)	14.0	1.8	14.0	1.5	14.1	2.0	0.95
	Median	IQR	Median	IQR	Median	IQR	
Smoking pack years	49	32—71	48	32—56	49	32—82	0.29
Annual exacerbation incidence/yr	2	0—3	3	2—4	1	0—2	<0.001
MRC dyspnoea	3	2—4	3	2—4	3	2—4	0.83
SaO_2 (% on air)	95	94—96	95	94—96	95	94—97	0.47
CRP (mg/l)	4	2—7	4	2—6	5	2—8	0.59

Table 2 Characteristics of 107 stable COPD patients compared with 30 control subjects.

	107 stable COPD patients		30 Control patients		Comparison of stable characteristics
	Mean	SD	Mean	SD	*p* value
Age (years)	69.4	8.2	68.6	6.1	0.61
FEV_1 (litres)	1.3	0.6	2.3	0.8	< 0.001
FEV_1 (% of predicted)	53.1	21.1	94.1	16.9	< 0.001
FVC (litres)	2.8	1.0	3.0	1.0	0.38
BMI (kgm^{-2})	25.9	5.4	26.3	6.0	0.74
FACIT-Fatigue Scale	35.3	11.0	43.2	10.5	0.001
VAS (0—10 cm)	4.4	2.3	0.6	1.2	< 0.001
TOTAL SGRQ score	49.2	18.0	13.2	17.7	<0.001
Activity domain	65.2	23.0	19.3	23.4	<0.001
Impact domain	36.1	19.3	7.7	15.3	<0.001
Symptom domain	62.3	20.0	19.9	24.9	<0.001
	Median	IQR	Median	IQR	
CES-D scale	11.0	5.0—20.0	7.5	3.0—11.0	0.026
Smoking pack years	49	32—71	15	0—34	<0.001
MRC dyspnoea	3	2—4	1	1—1	<0.001
SaO_2 (% on air)	95	94—96	96	96—97	0.001

follow-up. A p-value < 0.05 was taken as statistically significant for all tests.

Results

Patient characteristics

Table 1 shows the stable characteristics for 107 COPD patients (64 male), and a comparison of stable characteristics of a subset of 32 COPD patients seen at exacerbation with the remaining 75 COPD patients seen only when stable. Compared with patients who were not seen at exacerbation, patients seen at exacerbation were significantly younger, had a higher annual exacerbation incidence and poorer health status.

The stable characteristics of 107 COPD patients are compared with 30 control subjects in Table 2. These two groups were age-matched, but the COPD patients had a higher smoking pack year history. Patients with COPD had increased fatigue compared to control patients (thus a lower mean fatigue score of 35.3 units (SD 11.0) versus 43.2 (10.5), $p = 0.001$); median values were 37 (IQR 28—44) compared to 45 (39—50) respectively.

Fatigue in stable COPD

There was no relationship between fatigue and severity of COPD. In 107 stable COPD patients, fatigue was unrelated to FEV_1 ($r = 0.1$; $p = 0.3$), FEV_1 % predicted ($r = 0.1$; $p = 0.2$), and FVC ($r = 0.2$; $p = 0.1$). There was also no association between fatigue and GOLD staging (ANOVA $p = 0.07$) or oxygen saturation ($r = -0.1$; $p = 0.5$).

However, increase in fatigue in COPD was significantly related to increased perception of dyspnoea when assessed by the MRC Dyspnoea scale (ANOVA $p < 0.001$, Fig. 1) or VAS ($r = -0.34$; $p < 0.001$). Fatigue was also related to reduced quality of life (higher total SGRQ, $r = -0.61$; $p < 0.001$, Fig. 2), and to the activity, impact and symptom domains of the SGRQ ($r = -0.44$; $r = -0.65$; $r = -0.36$ respectively, and $p < 0.001$ for all three domains).

In stable patients, higher fatigue was related to higher depressive symptoms score ($r = -0.59$; $p < 0.001$, Fig. 3). A depression score consistent with clinical depression (CES-D $\geq$16) was associated with greater fatigue (mean 27.6 units (SD 10.7) versus 40.0 (8.4); $p < 0.001$).

The mean daily time spent outdoors was 3.0 h (2.3). Increased fatigue was related to reduced time spent outdoors ($r = -0.43$, $p < 0.001$). On multiple regression analysis of factors associated with time spent outdoors, increased fatigue remained the only factor significantly associated with reduced time spent outdoors (Table 3).

COPD patients with a history of ischaemic heart disease had greater fatigue 30.0 (13.5) than remaining patients at 36.2 (10.4), $p = 0.04$. However, on multiple regression

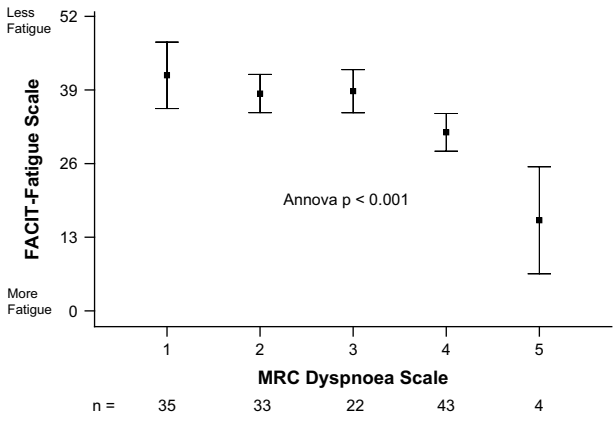

Figure 1 Box plot showing fatigue (mean and standard error, SEM) in patients with COPD at different levels of dyspnoea.

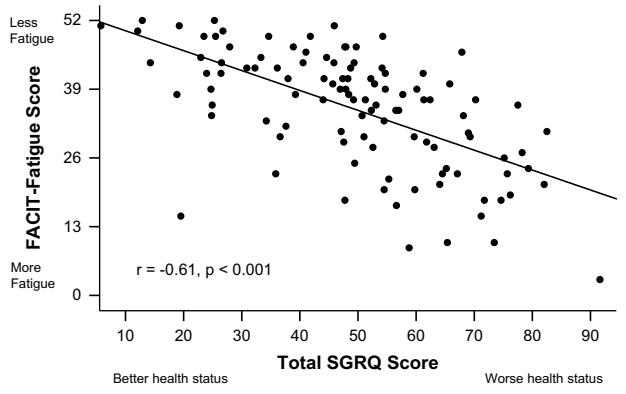

Figure 2 Scatter plot showing correlation between fatigue and health status in COPD.

analysis (Table 4), the association between fatigue and IHD was not statistically significant after allowance for other related factors. There was no association between fatigue and sex, current smoking status, smoking pack years, other comorbidities, levels of Hb or CRP, $p > 0.05$.

Fatigue and COPD exacerbation

Higher annual exacerbation frequency in stable patients was related to increased levels of fatigue ($r = -0.27$; $p = 0.005$). Fig. 4 shows that frequent exacerbators were significantly more fatigued than infrequent exacerbators ($p = 0.002$).

Increase in fatigue was a common feature of exacerbation (31/32 patients) at 4.3 (2.9) days from the onset of exacerbation symptoms. Compared to stable values, at exacerbation there was an overall increase in fatigue of 8.3 units (5.9) $p < 0.001$, Fig. 5; median values were 37 (28–44) in stable patients and 25 (18–32) at exacerbation. Fatigue at exacerbation was related to stable levels, $r = 0.81$, $p < 0.001$.

At exacerbation there was a significant increase in depression of 6.9 units (10.1), $p = 0.003$. Fatigue and depression at exacerbation were related ($r = -0.66$; $p < 0.001$) and the increase in fatigue at exacerbation was related to change in depression ($r = -0.46$; $p = 0.008$).

Exacerbation was associated with a reduction in FEV_1 of 0.13 l (0.28), $p = 0.006$. Increase in fatigue at exacerbation compared to the stable state was related to the reduction in FEV_1 ($r = 0.36$; $p = 0.04$) at exacerbation.

In 17 patients, who attended clinic 6 weeks post exacerbation onset, without an intervening exacerbation, fatigue was not significantly different from stable levels ($p = 0.53$, Fig. 5).

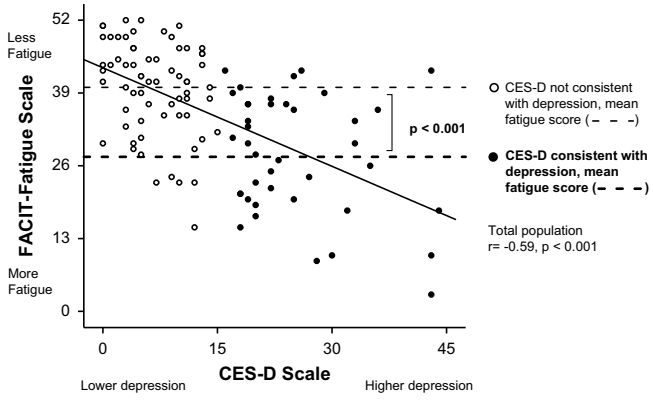

Figure 3 Scatter plot showing correlation between levels of fatigue and depression scales, and fatigue scores in patients who had a CES-D consistent with depression compared to others.

Table 3 Multiple regression analysis of factors associated with reduced time spent outdoors in COPD.

	Regression coefficient	Standard error	*p* value
FACIT-Fatigue scale	0.36	0.03	0.007
CES-D score	−0.06	0.03	0.89
FEV_1 % of predicted	0.11	0.01	0.32
Total SGRQ	0.13	0.02	0.43
MRC dyspnoea scale	−0.28	0.29	0.054

Discussion

In this study, we have demonstrated that the perception of fatigue in stable COPD was increased compared to age-matched control subjects. Increased fatigue in COPD was related to impairment of other important outcome measures such as dyspnoea, exacerbation frequency, health status and time spent outdoors, but not disease severity as assessed by FEV_1 or GOLD staging. At exacerbation there was a significant increase in the level of fatigue, related to a reduction in FEV_1. Patient fatigue recovered 6 weeks post exacerbation.

The perception of fatigue, whether due to mental or physical exhaustion, is a recognised symptom in the general population and a feature of chronic diseases.[28,29,36–38] The median fatigue of 37 units in our cohort of stable COPD patients was higher than in control subjects at 45, and higher than values reported by Cella[30] for the general population at 47 and non-anaemic patients with cancer at 42. At exacerbation the level of fatigue in COPD patients, at a median of 25 units, was comparable with that found in anaemic patients with cancer at 23.[30] These findings

Table 4 Multiple regression analysis of factors associated with fatigue in COPD.

	Regression coefficient	Standard error	*p* value
Time spent outdoors	1.23	0.42	0.004
Visual analogue score of dyspnoea	−1.18	0.42	0.007
Annual exacerbation frequency	−0.99	0.46	0.033
Depression (CES-D score)	−0.37	0.09	<0.001
IHD	−4.40	2.42	0.073

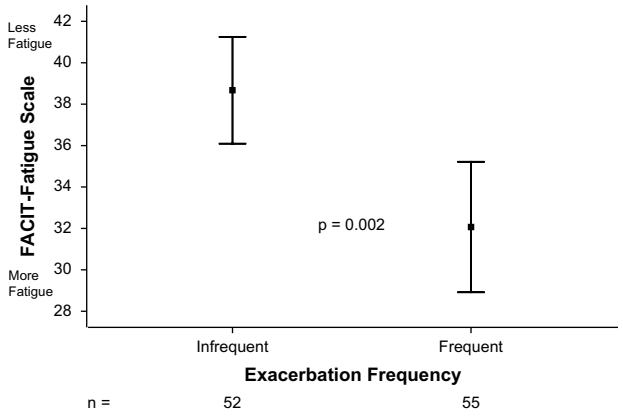

Figure 4 Relationship between stable fatigue levels (mean and SEM) and exacerbation frequency.

suggest that fatigue is increased and clinically relevant both in stable COPD and at exacerbation.

In stable patients, we did not find a relationship between the perception of fatigue and FEV_1 or GOLD staging. This lack of correlation between fatigue and severity of disease in stable patients may be related to an adaptation to chronic impairment. The increase in fatigue at acute exacerbation was related to change in FEV_1. Dyspnoea at COPD exacerbation is predominantly related to a reduction in vital capacity of lungs due to dynamic hyperinflation,[39,40] which is better reflected by a reduced inspiratory capacity (IC) than by change in FEV_1. Since the perceptions of dyspnoea and fatigue are related, we speculate that a mechanism of increase in fatigue at exacerbation may be an increase in work of breathing through a similar pathway, and that increase in fatigue at exacerbation may also therefore be more closely related to change in IC than FEV_1.

Fatigue in COPD forms an important component of health status,[5] which is reduced at exacerbation.[12,41] This study was not designed to detect a clinically significant change in fatigue, but we estimated that an increase in fatigue of 1.50 units would be associated with a four point increase in the total SGRQ scale, accepted as the minimum clinically significant change in health status.[42] Our finding

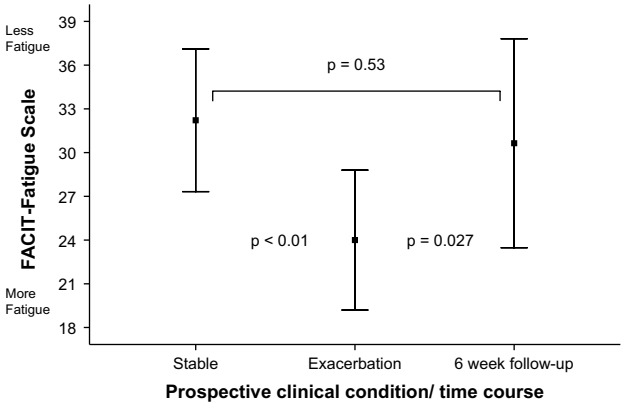

Figure 5 Box plot showing fatigue (Mean and SEM) at exacerbation and on follow-up in 17 patients with COPD.

of an 8 unit increase in fatigue at exacerbation may therefore be related to a very significant reduction in health status during exacerbation. Fatigue may contribute to the morbidity and healthcare costs[21] associated with exacerbations.

The level of fatigue in stable patients correlated with fatigue at exacerbation. Therefore, if fatigue is an important determinant of activity and increased need for social support, monitoring fatigue may allow early identification of COPD patients who are most likely to benefit from community support, facilitated discharge from hospital, or therapy directed at fatigue (discussed later).

We and others[6] have shown a relationship between fatigue and depression in COPD, which persists at exacerbation. It should be noted that our assessment of depression was independent of somatic symptoms such as fatigue and that the FACIT-Fatigue scale provides a measure of performance status due to fatigue symptoms. Whether fatigue is a cause or symptom of depression, effective strategies need to be developed to address fatigue and associated physical inactivity in addition to any underlying depression.

Fatigue recovered to stable levels within 6 weeks of COPD exacerbation, in patients without an intervening exacerbation. The number of non-recovered exacerbations was two, and a further 8 patients had recurrent exacerbation within 6 weeks. We were therefore unable to form any conclusion on the relevance of fatigue in persistent exacerbation. In stable COPD, increase in fatigue was related to increase in exacerbation frequency. The relationship between fatigue and exacerbation frequency may be due to increase in physical inactivity at and around exacerbation,[10,11] propagating a downward cycle of muscle de-conditioning, further fatigue, and weakness which has been associated with recurrent exacerbation,[11] healthcare utilization[17] and increased mortality.[18] These findings are supported by our finding that an increase in the perception of fatigue was related to a reduction in mean time spent outdoors, an indicator of physical activity, and a reduction in activity related health status. The relevance of the perception of fatigue in COPD is underlined by our finding on multiple regression analysis that fatigue remained the only factor significantly related to time spent outdoors (Table 3). However, we acknowledge that reported time spent outdoors does not measure different levels of physical activity.

There was no evidence of a relationship between fatigue in stable COPD and CRP levels, consistent with the suggestion that systemic inflammation does not play a part in the pathophysiology of fatigue. Fatigue in COPD was associated with a history of ischaemic heart disease (IHD), but this relationship was not significant in a multiple regression analysis (Table 4). Fatigue is a recognised feature of congestive cardiac failure (CHF) but not IHD, and this study was not designed to evaluate the role of fatigue in patients with COPD and coexisting CHF.

Exercise training as part of pulmonary rehabilitation leads to significant improvement in functional exercise capacity and health status in stable COPD.[19–21] These beneficial effects have also been demonstrated following COPD exacerbation.[43] There is evidence to suggest that exercise rehabilitation may also reduce fatigue (indicated

by an increase in the fatigue domain of the CRQ,[19,43]), emergency hospital admission[43] and days spent in hospital[19] following subsequent exacerbation. Early recognition of fatigue in patients with COPD, may therefore allow identification of patients who are likely to benefit from implementation of early exercise rehabilitation, prior to hospitalisation and progression of morbidity associated with inactivity. Our study suggests that assessment of fatigue in COPD patient may serve as an important indicator of physical inactivity (Table 3) and coexisting depression (Fig. 3) which should be addressed. Further research is needed to determine the optimal mode and frequency of exercise training, and to investigate other strategies for reducing fatigue in COPD.

Conflict of interest statement

None of the authors have a conflict of interest to declare in relation to this work.

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