Factors associated with experience of fatigue, and functional limitations due to fatigue in patients with stable COPD

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Abstract

Background: The aim of this study was to determine the influence of selected physiological, psychological and situational factors on experience of fatigue, and functional limitations due to fatigue in patients with stable chronic obstructive pulmonary disease (COPD).

Methods: In total 101 patients with COPD and 34 control patients were assessed for experience of fatigue, functional limitation due to fatigue (Fatigue Impact Scale), physiological [lung function, 6-minute walk distance (6MWD), body mass index (BMI), dyspnoea, interleukin (IL)-6, IL-8, high sensitivity C-reactive protein (hs-CRP), surfactant protein D], psychological (anxiety, depression, insomnia), situational variables (age, sex, smoking, living alone, education), and quality of life.

Results: Fatigue was more common in patients with COPD than in control patients (72% *versus* 56%, $p < 0.001$). Patients with COPD and fatigue had lower lung function, shorter 6MWD, more dyspnoea, anxiety and depressive symptoms, and worse health status compared with patients without fatigue (all $p < 0.01$). No differences were found for markers of systemic inflammation. In logistic regression, experience of fatigue was associated with depression [odds ratio (OR) 1.69, 95% confidence interval (CI) 1.28–2.25) and insomnia (OR 1.75, 95% CI 1.19–2.54). In linear regression models, depression, surfactant protein D and dyspnoea explained 35% (R^2) of the variation in physical impact of fatigue. Current smoking and depression explained 33% (R^2) of the cognitive impact of fatigue. Depression and surfactant protein D explained 48% (R^2) of the psychosocial impact of fatigue.

Conclusions: Experiences of fatigue and functional limitation due to fatigue seem to be related mainly to psychological but also to physiological influencing factors, with depressive symptoms, insomnia problems and dyspnoea as the most prominent factors. Systemic inflammation was not associated with perception of fatigue but surfactant protein D was connected to some dimensions of the impact of fatigue

Keywords: chronic obstructive pulmonary disease, fatigue, symptoms, systemic inflammation

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Introduction

Fatigue is the second most common and distressing symptom in patients with chronic obstructive pulmonary disease (COPD), with a prevalence ranging between 47% and 71% in different studies [Theander and Unosson, 2004; Jablonski *et al.* 2007; Walke *et al.* 2007; Blinderman *et al.* 2009]. Fatigue affects health status and can predict mortality among patients with COPD [Andersson *et al.* 2015]. Despite the high prevalence and significant consequences such as impaired quality of life and increased risk of hospitalization [Breslin *et al.* 1998; Kapella *et al.* 2006; Theander *et al.* 2008; Baltzan *et al.* 2011; Peters *et al.* 2011; Paddison *et al.* 2012], fatigue in patients with COPD is often neglected [Lewko *et al.* 2009]. The aetiology and mechanisms responsible for fatigue are probably complex and multifactorial and are currently not fully understood [Davis and Walsh, 2010], and as a consequence knowledge

about treatment options is limited. A better understanding of the aetiology of fatigue will improve the basis for prevention and treatment of this distressing symptom.

There is no consensus definition of fatigue. According to the definition of Ream & Richardson, fatigue is a multidimensional phenomenon: a 'subjective, unpleasant symptom that incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition, which interferes with individuals' ability to function to their normal capacity' [Ream and Richardson, 1996]. Importantly, this definition comprises both the experience and impact of fatigue. Some studies have focused on the experience of fatigue [Breslin *et al.* 1998; Kapella *et al.* 2006], while others have examined the impact of fatigue [Baghai-Ravary *et al.* 2008] . Physiological, psychological and situational factors are supposed to influence the experience of any symptom [Lenz *et al.* 1997], and as such are essential to evaluate in exploring COPD-associated fatigue and the impact of fatigue in patients. Among physiological factors, exercise capacity and muscle function are reported to be related both to the experience of fatigue and the impact of fatigue [Breslin *et al.* 1998; Breukink *et al.* 1998; Inal-Ince *et al.* 2010; Calik-Kutukcu *et al.* 2014], whereas the relation to lung function is contradictory [Breslin *et al.* 1998; Oh *et al.* 2004; Kapella *et al.* 2006; Baghai-Ravary *et al.* 2008; Lewko *et al.* 2009].

Increasing observations indicate that COPD is a complex inflammatory disease involving more than airflow obstruction [Agusti, 2007]. Various systemic manifestations are recognized in which fatigue is one of the most important symptoms. Several of these COPD-related systemic manifestations and symptoms are assumed to be secondary to inflammation [Barnes and Celli, 2009]. Proinflammatory cytokines are also proposed to have a central role in the development of 'sickness behaviour', which includes symptoms such as fatigue, sleep problems and depression [Dantzer *et al.* 2008]. In COPD, the most widely studied systemic inflammatory biomarkers are C-reactive protein (CRP) and interleukin (IL)-6 [Barnes and Celli, 2009]. Increased CRP is related to health status and exercise capacity but no clear relation to fatigue has been found. [Broekhuizen *et al.* 2006; Baghai-Ravary *et al.* 2008]. Higher serum levels of inflammation markers such as IL-6 are linked with feelings of fatigue in healthy men, and in studies of healthy individuals the injection of low-dose recombinant human IL-6 is associated with increased fatigue [Spath-Schwalbe *et al.* 1998]. However, neither CRP nor IL-6 are lung-specific biomarkers. Surfactant protein (SP-D) is a more lung-specific biomarker which is elevated in patients with stable COPD, indicating a pulmonary origin of systemic COPD inflammation [Sin *et al.* 2008]. In patients with stable COPD, SP-D positively correlates with disease severity expressed as forced expiratory volume in 1 second (FEV_1)% predicted and BODE (body mass index, airflow obstruction, dyspnoea, and exercise capacity) index [Ju *et al.* 2012]. In contrast, the association between symptoms like dyspnoea, health-related outcomes and SP-D is contradictory [Sin *et al.* 2007; Liu *et al.* 2014]. There are only a few reports on the experience of fatigue and systemic inflammation in people with stable COPD [Garrod *et al.* 2007; Al-Shair *et al.* 2011] and no studies have been recognized to evaluate the relation between SP-D and experience of fatigue or impact of fatigue in patients with stable COPD.

Psychological factors such as anxiety, depression and sleep disorders are common among patients with COPD [Blinderman *et al.* 2009], as well as among elderly in general [Loge *et al.* 1998; Ohayon and Bader, 2010; Grav *et al.* 2012]. Anxiety, depression and sleep quality are reported to be associated with fatigue in COPD [Breslin *et al.* 1998; Kapella *et al.* 2006; Lewko *et al.* 2009]. Previous studies also show that situational factors, such as age and gender, are connected with the experience of fatigue among patients with COPD [Gift and Shepard, 1999; Kapella *et al.* 2006; Lewko *et al.* 2009; Wong *et al.* 2010; Baltzan *et al.* 2011]. Even though earlier studies report relationships between fatigue and some physiological, psychological and situational factors, few studies test all these variables comprehensively in a model of stable COPD patients.

The aim of the present study was to evaluate fatigue and factors potentially associated with experience of fatigue in a group of patients with stable COPD and a group of control patients. Further, within the COPD sample we aimed to determine the influence of selected physiological, psychological and situational factors on fatigue, and functional limitations due to fatigue.

Methods

Design

This study was a cross-sectional and comparative study including 101 patients with COPD and 34 control subjects. Both populations are described in detail below. The data reported in this article were collected as part of a previously published study [Todt *et al.* 2014]. The study protocol was approved by the Regional Ethical Review Board, Dnr M121-06 and 21-07

Selection of patients

Patients treated and registered for COPD during the previous year at two outpatient departments, one university hospital and one county hospital were consecutively identified through the patient administrative system. Inclusion criteria were: diagnosis of COPD with a post-bronchodilation FEV_1 to forced vital capacity (FVC) ratio, FEV_1/FVC < 0.7. In addition, included patients were in a clinically stable condition, thus, no changes in medication were made during the 4 weeks preceding inclusion. Exclusion criteria were: any other lung disease, cancer in the past 5 years, known inflammatory disease (e.g. rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis), stroke, severe ischemic heart disease, severe kidney dysfunction, insulin-dependent diabetes or psychosocial or physical difficulties that might interfere with the assessments.

In total, 198 patients were invited by an information letter and contacted within a week for additional information, interview and informed consent. Of those who were willing to participate ($N = 137$), 16 were excluded, while 121 underwent assessments at the outpatient department. There were no differences in age or gender between participating and nonparticipating patients. Since the first 20 patients included in the study were not assessed with all variables, only 101 patients are reported in this paper (Figure 1).

Selection of control group

The control group was randomly selected from the general population register from the same geographical area as the patients with COPD, and matched for age (± 5 years) and gender against 40 randomly selected included patients. In total, 147 patients were invited. Of those, 68 declined to participate and 20 did not answer. Those 59 who gave informed consent were contacted by telephone for additional information and interviewed for inclusion and exclusion criteria. Control patients with self-reported COPD were not included. The exclusion criteria were exactly the same as for the patients. Of the 59 patients willing to participate, 16 did not fulfil criteria. Of the remaining 43 patients, a further 9 were excluded, due to FEV_1/FVC ratio < 0.70. In total 34 control patients (14 men) are reported in this study (Figure 1). Importantly, the control patients cannot be regarded as a healthy control group. They were not sampled as healthy old people but rather selected from the general population using the same criteria as for the participants with the exception that patients with COPD were excluded.

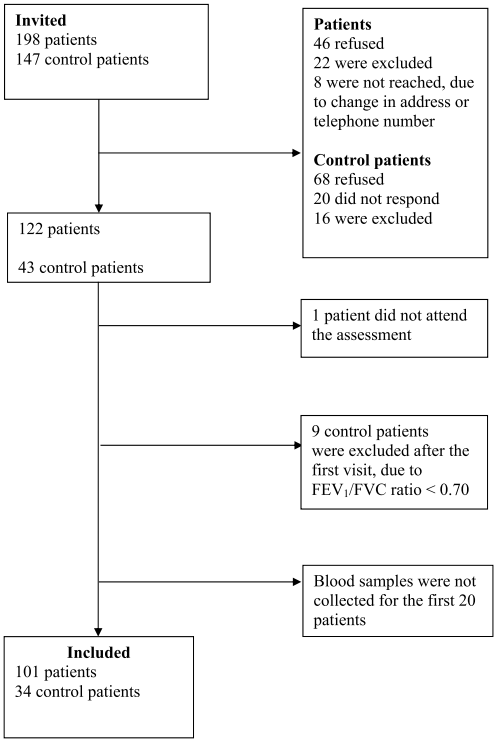

Figure 1. Flow chart of recruitment and inclusion of patients with COPD and a control group selected from the general population.
COPD, chronic obstructive airways disease; FEV_1 forced expiratory volume in 1 second; FVC, forced vital capacity.

Measures

Fatigue and the impact of fatigue. Experience of fatigue was assessed with three separate slightly revised structured questions used in earlier study

[Theander and Unosson, 2004]. Respondents were asked to rate the frequency (0 = not a problem; 1 = 1–7 days/month; 2 = 8–14 days/month,;3 = 15–21 days/month; 4 = 22–30 days/month or every day), duration (0 = no experience; 1 = less than 6 hours/day; 2 = 6–12 hours/day; and 3 = >12 hours/day) and severity (0 = not a problem; 1 = one of my less severe symptoms; and 2 = one of my worse symptoms) of fatigue during the last month. The fatigue sum scores range between 0–9. In the present study, Cronbach's alpha reliability for those three questions was 0.79. Convergent validity examined by correlation analysis between total sum score for fatigue and total score for lack of energy assessed by using Memorial Symptom Assessment [Portenoy *et al.* 1994] scale in the present study was satisfactory (r_s = 0.658) [Todt *et al.* 2014]. Patients and control patients reporting fatigue score ⩾1 were classified as those with fatigue, and 0 scores = with no fatigue.

The impact of fatigue on functioning in daily living was assessed using the Fatigue Impact Scale (FIS) [Fisk *et al.* 1994]. FIS comprises 40 items in three dimensions, physical (10 items), psychosocial (20 items) and cognitive (10 items). Each item is scored from 0 (= no problem) to 4 (= extreme problem). Higher scores indicate greater functional limitations in daily life activities due to fatigue. The wording of each item starts with 'because of my fatigue, I am…' and supposes that the respondents have experienced some fatigue during the past month, including on the day of the testing. To use the scale in a reliable way, patients and control patients who did not experience fatigue were not required to respond to this questionnaire. The internal consistency of the FIS has been tested among patients with COPD, and the Cronbach's alpha for the total scale was 0.98, and >0.87 for the different dimensions [Theander *et al.* 2007]. The internal consistency (Cronbach's alpha) for the dimensions of FIS in the present study ranged between 0.94–0.95.

Health status. Health status among patients with COPD was assessed by using the validated Swedish version of St George's Respiratory Questionnaire (SGRQ) [Engstrom *et al.* 1998]. The SGRQ consists of 76 items (developed to measure health status in patients with diseases of airways obstruction) in three domains: symptoms, impact and activity. The scores for each dimension are in the range 0–100, and higher scores indicate worse health status.

Physiological measures

The dynamic lung function test (Master Scope® Jaeger, Germany) was performed pre- and post-bronchodilation (0.6 mg salbutamol dosaerosol + spacer) according to ATS/ERS guidelines [Brusasco *et al.* 2005]. The normative values from Hedenstrom and colleagues [Hedenstrom *et al.* 1985; Hedenstrom *et al.* 1986] were used. Body mass index (BMI) was calculated as weight in kg/(height in m)^2. Exercise capacity was assessed with six-minute walking distance (6MWD) performed twice in accordance with the ATS guidelines [American Thoracic Society, 2002]. The best results from the two tests were used in the analysis. Experience of dyspnoea was measured by the modified Medical Research Council (mMRC) scale [Bestall *et al.* 1999] including five statement of different degrees of dyspnoea during certain activities. The possible grade range between 0 (breathlessness with strenuous activities) and 4 (breathlessness when putting on clothes or too breathless to leave the house). In the present study, scores ⩾2 was used to characterize patients with 'more breathlessness' dyspnoea and scores ⩽1 as 'less breathless' according to Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD guidelines (2016 [1997]).

Fasting blood samples were collected by a registered nurse in the morning (08.00–10.00 a.m.), and plasma was obtained by centrifugation at 1500 × *g* for 15 minutes at room temperature. The samples were stored at −70°C until analysis. CRP concentration was analysed with a microparticle-enhanced immunoturbidimetric method using an automated clinical chemistry analyser (Advia Chemistry System 1800, Bayer HealthCare AG, Germany). A combination of normal and high sensitivity (hs) methods was used with an analytical range for CRP of 4–304 mg/l, and 0.36–10 mg/l for hs-CRP. Surfactant protein D (SP-D) was determined by using a commercially available ELISA kit (Biovendor, Germany) according to the manufacturer's instructions. The optical density was measured by using microplate reader (BEP fully automated ELISA processor, Dade Behring, Germany). The detection limit for SP-D was 1.6 ng/ml.

Cytokine concentrations in plasma were measured by Luminex multiple bead technology (Custom Human 4 -plex High Sensitivity Cytokine Panel, Biolegend, San Diego, CA, USA) according to the manufacturer's instructions. Tumour necrosis factor (TNF)-α, IL-1β, IL-6, IL-8 were measured. The lower detection limits for IL-1β

and TNF-α were 1.28 pg/ml and for IL-6 and IL-8 0.26 pg/ml. Values under the detection limit were given half the value of the lowest detection limit (i.e. 0.64 and 0.13 pg/ml respectively). Among the patients, some cytokines were hardly detectable in plasma. Thus, IL-1β was detectable in18 patients and TNF-α in 16 patients, consequently, no further statistical calculations were performed on these cytokines.

Psychological measures

Anxiety and depressive symptoms were assessed by the Swedish validated version of the Hospital Anxiety and Depression Scale (HADS) [Zigmond and Snaith, 1983; Lisspers *et al.* 1997]. The questionnaire is used for screening and comprises 14 items; 7 items measure anxiety and 7 items measure depression. Each item is rated on a 4-point scale (0–3) with total scores ranging between 0–21, with the higher score indicating higher symptom levels. A cut-off value of ⩾8, on both the anxiety and depression subscales, distinguishes patients with and without clinically relevant symptoms [Zigmond and Snaith, 1983]. Symptoms of insomnia during the last month were measured by using the Minimal Insomnia Symptom Scale (MISS) measuring the problems with difficulty falling asleep, night awakenings and not being rested by sleep. Each item was scored from 1 (no problem) to 5 (very severe problem), with a total score ranging from 3–15. Scores ⩾6 were used to define patients with clinical insomnia [Broman *et al.* 2008].

Situational measures

All patients completed a questionnaire to provide information on their age, gender, education, marital status, living alone/cohabiting, current employment and smoking status (current smoker, former smoker, never smoker and number of pack-years).

Procedure

Participants were scheduled for an appointment at the outpatient department. Questionnaires were added to the letter with the time for appointment, including instructions to fill in the forms the day before the appointment and bring them back when visiting the department. All other assessments were performed in the morning (between 08.00 and 10.00 a.m.) at one appointment at an outpatient clinic. The assessments were performed in a standardized order (collection of blood samples, dynamic spirometry, two 6MWD tests with 30 minutes apart). Data collection was performed between January 2007 and September 2009.

Statistical analysis

Data are presented as the mean and standard deviation (± SD), median (Md) and interquartile range (IQR). Differences between patients with COPD and control patients as well as patients with fatigue and without fatigue were examined with Chi-square test (nominal data), Mann–Whitney *U* test (ordinal or non-normal distributed interval or ratio data) or Student's *t*-test for independent groups (interval or ratio data with normal distribution). Odds ratio (OR) with 95% confidence interval (CI) for experience of subjective fatigue (1 = fatigue sum score of ⩾1 or 0 = zero sum score) within COPD patients was calculated from the multiple logistic regression analysis (backward selection method). Independent variables were those that were significantly ($p < 0.05$) correlated (Pearson product moment correlation coefficient) with total scores of subjective fatigue (6MWD, HADS anxiety and depressions scale and MISS insomnia scale), or were significantly different (Mann–Whitney *U* test) between those with or without dyspnoea (coded as 1 = mMRC grade ⩾2 or 0= mMRC grade ⩽1) and with completed high school or higher education (coded as 1 = yes, 0 = no).

In the final analysis of systemic inflammation markers, one outlier was excluded for CRP, two for SP-D, one for IL-6 and finally two for IL-8.

To identify factors independently related to the impact of fatigue within the COPD group, we conducted three separate multiple linear regression models with a backward selection method on the physiological, psychosocial and cognitive dimensions of FIS.

To recognize potential factors related to impact of fatigue we used univariate analysis between scores of each dimension and investigated each variable using Pearson product moment correlation or Mann–Whitney U test, where appropriate. Variables having p value < 0.200 in the univariate analysis were then included in the multiple linear regression analysis. To detect multicollinearity between independent variables the variance inflation factor (VIF) was computed. All statistical

tests were two-sided and the tests were considered significant when $p < 0.05$ [Field, 2009]. Statistical analysis was performed with the PASW Statistics package (version 21.0, SPSS).

Results

Differences between patients with COPD and control group

The prevalence of fatigue was 72% among patients with COPD compared with 56% among control patients ($p = 0.010$) with a median (IQR) total score of 7 (4) for the patients and 4 (2) for the control group ($p < 0.001$). The characteristics of the patients with COPD and the control group are shown in Table 1. The group of patients and the control group were similar in terms of age (mean 68 and 67 years respectively) and sex but there was a higher proportion of current and former smokers and a lower proportion currently in employment among the patients with COPD (Table 1). The majority of the patients, 80%, were classified as GOLD stages II and III, and 15% were GOLD stage IV. Compared with the control group the patients with COPD had significantly higher scores for dyspnoea and depression symptoms and also displayed higher concentrations of systemic inflammatory markers IL-6 and CRP, while there was no difference for IL-8 and surfactant protein D (Table 1).

The patients with COPD had significantly higher scores for frequency, duration and severity of subjective fatigue than the control group (Table 2). Overall 48% of the patients and 21% of the control group reported that fatigue was one of their worst symptoms. Compared with patients in the control group reporting fatigue, the patients with fatigue had greater limitation on physical and psychosocial functioning due to fatigue, but not on the cognitive functioning (Table 2).

Factors associated with fatigue in patients with COPD

Patients reporting fatigue, compared with patients without fatigue, had significantly lower education, worse lung function, lower exercise capacity and higher symptom levels for dyspnoea, anxiety, depression and insomnia (Table 3). Of the patients with fatigue, 24 (33%) had clinically relevant depressive symptoms (HADS score $\geqslant 8$), 27 (38%) had anxiety and 47 (64%) had insomnia (MISS $\geqslant 8$), while among patients without fatigue the corresponding figures were one (4%), two (7 %) and 4 (14%), respectively. Multiple logistic regression analysis showed that depression and insomnia were independently associated with fatigue, with ORs (95% CI) of 1.69 (1.28–2.25), $p < 0.001$ for depression and 1.75 (1.19–2.54), $p = 0.004$ for insomnia. Health status was worse in all domains in patients with fatigue than in those without fatigue (Table 3).

Factors associated with the impact of fatigue in patients with COPD

Potential factors related with physical, psychological and cognitive dimension of FIS are shown in Table 4. The physical dimension of FIS was related ($p < 0.200$) to FEV_1, 6MWD, SP-D, anxiety and depression and significant different according to current smoking with worse impact of fatigue in patients with ongoing smoking. Patients with more pronounced dyspnoea (mMRC $\geqslant 2$) had greater limitation on physical and psychosocial dimension of FIS than those with less dyspnoea (mMRC $\leqslant 1$). The psychosocial dimension of FIS was significantly related with age, pack-years, FEV_1, 6MWD, SP-D, insomnia, anxiety and depression. The cognitive dimension of FIS was related with age, pack-years, anxiety, depression and insomnia. Patients with current smoking had more limitation on cognitive functioning than those who had stopped smoking or never smoked.

The multiple linear regression models performed for each dimension of FIS showed that dyspnoea, depression and SP-D explained 35% (R^2) of the variance in the physical dimension of FIS. Depression, anxiety and SP-D, explained 48% (R^2) of the variance in the psychosocial dimension of FIS and depression, and current smoking explained 33% (R^2) of the variance in the cognitive dimension of FIS (Table 5).

Discussion

The present study examined the relationships between selected physiological, psychological and situational factors to experience of fatigue, and evaluated the impact of fatigue on functioning in daily living among patients with stable COPD. The main results were that patients with COPD and fatigue had lower lung function, shorter 6MWD, more dyspnoea, depression and insomnia symptoms and worse health status than those

Table 1. Characteristics in patients with chronic obstructive pulmonary disease (COPD) and a control group.

Characteristics	**COPD group (*n* = 101)**	**Control group (*n* = 34)**	*p*-value[1]
Situational			
Age (yrs), mean (SD)	68 (7)	67 (7)	0.62
Sex, male, *n* (%)	49 (49)	14 (59)	0.46
Smoking habit, *n* (%)			
Current	23 (23)	4 (12)	**<0.001**
Former	76 (75)	14 (41)	
Never smokers	2 (2)	16 (47)	
Pack-years*, mean (SD)	33 (18)	9 (13)	**<0.001**
Living alone, *n* (%)	29 (29)	9 (27)	0.48
Employment, *n* (%)	15 (15)	14 (41)	**0.005**
Education: Completed high school or higher *n* (%)	33 (33)	13 (38)	0.55
COPD GOLD stage, *n* (%)			
Stage I ($FEV_1 > 80\%$ of predicted value)	6 (6)		
Stage II (FEV_1, 50–80% of predicted value)	38 (38)		
Stage III (FEV_1, 30–50% of predicted value)	42 (42)		
Stage IV ($FEV_1 \leqslant 30\%$ of predicted value)	15 (15)		
Physiological,	mean (SD)	mean (SD)	
FEV_1 (% predicted)	50 (17)	98 (11)	**<0.001**
FVC (% predicted)	87(18)	98 (13)	**<0.001**
FEV_1/FVC	0.44 (0.1)	0.75 (0.05)	**<0.001**
BMI (kg/m²)	26.7 (5.9)	25.6 (3.3)	0.55
6MWD (m)	395 (139)	562 (112)	**<0.001**
	Md (IQR)	Md (IQR)	
mMRC Dyspnoea grade (range 0–4)	2 (2)	1 (1)	**<0.001**
Interleukin-6 (pg/ml),	2.25 (3.49)	1.03 (1.8)	**0.001**
Interleukin-8 (pg/ml)	7.2 (4.9)	6.1 (3.8)	0.07
C-reactive protein (mg/l)	4.3 (4.9)	2.1 (1.3)	**<0.001**
Surfactant protein D (ng/ml)	84(62)	72 (55)	0.07
Psychological, Md (IQR)			
HADS anxiety score (range 0–21)	4 (7)	3 (5)	0.25
HADS depression score (range 0–21)	5 (6)	2 (3)	**0.001**
MISS insomnia score (range 3–15)	6 (4)	6 (5)	0.75

6MWD, six-minute walk distance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1 % predicted, forced expiratory volume over 1 second of predicted; FVC % predicted, forced volume capacity of predicted; HADS, Hospital Anxiety and Depression scale; IQR, interquartile range; Md, median; MISS, Minimal Insomnia Symptom scale; mMRC, modified Medical Research Council dyspnoea scale; SD, standard deviation

[1]*p* values are from Chi-square test (nominal data), Student's *t*-test (normally distributed data) or Mann–Whitney U test (not normally distributed data).

*Pack-year, number of years smoking × average number of cigarettes smoked per day /20.

patients with COPD without fatigue. Regression analysis suggested that the significant associates of fatigue included both physiological (i.e. dyspnoea, surfactant protein D), psychological factors (i.e. depressive and insomnia symptoms) and situational factors (current smoking). An association between systemic inflammatory markers and experience of fatigue was not demonstrated. The factors that influenced the impact of fatigue varied in different dimensions of the FIS, and the only generally-associated factors for all dimensions were depressive symptoms.

The main purpose of having a control group was to ensure that any potential differences regarding inflammation could be related to presence of COPD. As described in methods the control patients cannot be regarded as a healthy control

Table 2. Frequency, duration and severity of fatigue and impact of fatigue in patients with COPD and a control group with fatigue.

	COPD group with fatigue *n* = 73	Control group with fatigue *n* =19	*p*-value[1]
Frequency, n (%)			
1 = 1–7 days/month	19 (26)	9 (47)	**0.003**
2 = 8–14 days/month	6 (8)	5 (26)	
3 = 15–21 days/month	7 (10)	2 (11)	
4 = 22–30 days or every day of the month	41 (56)	3 (16)	
Duration, n (%)			
1 = <6 hours/day	36 (49)	13 (72)	**0.038**
2 = 6–12 hours/day	22 (30)	5 (28)	
3 ⩾12 hours/day	15 (21)	0 (0)	
Severity, n (%)			
0 = Not a problem	8 (11)	4 (21)	**0.032**
1 = One of my less severe symptoms	30 (41)	11(58)	
2 = One of my worst symptom	35 (48)	4 (21)	
Impact of fatigue, mean (SD)			
FIS physical (range 0–40)	20 (10)	7 (7)	<**0.001**
FIS psychosocial (range 0–80)	28 (18)	11 (14)	<**0.001**
FIS cognitive (range 0–40)	12 (9)	8 (6)	0.059

COPD, chronic obstructive pulmonary disease; FIS, Fatigue Impact scale; SD, standard deviation.
[1]*p* values are from Mann–Whitney U test and Student's *t*-test for independent groups.

group. They were selected from the general population using the same criteria as for the participants with the exception that patients with COPD were excluded. The control group and the participants were matched according to age and gender. The present study confirms findings in earlier studies that stable COPD patients express higher systemic inflammatory markers than age and gender matched control [Gan *et al.* 2004]. Fatigue was also a common symptom in the control group and this is in line with earlier population based studies in older cohorts [Loge *et al.* 1998]. Moreover, the experience of COPD related fatigue was significantly more frequent, more pronounced with both longer duration and severity. In similarity, the impact of the fatigue was more severe in the patients with COPD. These findings are in line with Kapella and colleagues and propose that there are unique features of COPD-related fatigue [Kapella *et al.* 2006].

Physiological factors

Dyspnoea, related to physical activity, regarded as one of the physiological factors, was significantly associated with physical aspects of fatigue. These findings are in agreement with earlier studies [Gift and Shepard, 1999; Woo, 2000; Reishtein, 2005; Kapella *et al.* 2006]. Dyspnoea seems to be important for the presence of fatigue and especially to the dimension of fatigue impact on physical function. Both can be important restrictors to physical activity [Todt *et al.* 2014]. Although, we found significant differences between patients with and without fatigue in important physiological variables such as lung function and exercise capacity, these variables, in contrast to dyspnoea, were not retained in the regression models, suggesting that the variables did not make a statistically significant contribution to how well the model predicted the impact of fatigue. Dyspnoea related to physical activity reflects disease severity as well as lung function and exercise capacity. Paddison and colleagues concluded that fatigue and BODE index [Celli *et al.* 2004], a composite measure including dyspnoea, BMI, airflow obstruction and exercise capacity, shared only 30–50% of variance, suggesting that there are other factors that define disease severity [Paddison *et al.* 2012]. A factor hypothesized to influence the experience and impact of fatigue was inflammation. In the present study we analysed different markers for systemic inflammation and for their relationship to fatigue. We found that patients with COPD had higher levels of systemic inflammatory markers than the control patients, which is consistent with earlier studies [Agusti *et al.* 2003; Gan *et al.*

Table 3. Situational, physiological and psychological characteristics and health status in COPD patients with or without fatigue.

Characteristics	Patients with COPD		*p*-value[1]
	With fatigue (*n* = 73)	**Without fatigue (*n* = 28)**	
Situational, *n* (%)			
Sex (male)	37 (51)	12 (43)	0.48
Current smoker	18 (25)	5 (18)	0.47
Living alone	21 (29)	8 (28)	0.93
Employment	11 (15)	4 (14)	0.83
Education: Completed High School or Higher	18 (25)	15 (54)	**0.006**
COPD GOLD stage			
Stage I and II ($FEV_1 > 50\%$ of pred. value)	28 (38)	16 (58)	0.09
Stage III and IV ($FEV_1 < 50\%$ of pred. value)	45 (62)	12 (43)	
Physiological	mean (SD	mean (SD)	
FEV_1 (% predicted)	47 (16)	56 (16)	**0.01**
FVC (% predicted)	84 (18)	94 (16)	**0.01**
FEV_1 /FVC ratio	0.43 (0.1)	0.46 (0.1)	0.14
BMI (kg/m²)	26.9 (6.3)	26.3 (4.8)	0.78
6MWD (m)	373 (142)	454 (114)	**0.01**
	Md (IQR)	Md (IQR)	
mMRC Dyspnoea grade (range 0–4)	2 (2)	1 (1)	**<0.001**
Interleukin-6 pg/ml	2.0 (3.5)	2.8 (3.4)	0.37
Interleukin-8 pg/ml	7.2 (4.4)	6.1 (5.4)	0.34
C-reactive protein mg/l	4.3 (4.2)	3.4 (6.6)	0.70
Surfactant protein D ng/ml	83 (56)	79 (96)	0.69
Psychological, md (IQR)			
HADS anxiety score (range 0–21)	5 (6)	2 (5)	**<0.001**
HADS depression score (range 0–21)	6 (4)	1 (3)	**<0.001**
MISS insomnia score (range 3–15)	7 (4)	4 (2)	**<0.001**
Health status, mean (SD)			
SGRQ symptoms (range 0–100)	55 (21)	26 (15)	**<0.001**
SGRQ activity (range 0–100)	68 (17)	47 (22)	**<0.001**
SGRQ impact (range 0–100)	42 (17)	15 (10)	**<0.001**

6MWD, six-minute walk distance; BMI, body mass index COPD, chronic obstructive pulmonary disease; HADS, Hospital Anxiety and Depression Scale; FEV_1 % predicted, forced expiratory volume over 1 second of predicted; FVC % predicted, forced volume capacity of predicted; IQR, interquartile range; Md, median; mMRC-dyspnoea score, modified Medical Research Council dyspnoea scale; SD, standard deviation; SGRQ, Saint George's respiratory questionnaire.
[1]p values are from Chi-square test (nominal data), Student's t-test (normally distributed data) or Mann-Whitney U test (not normally distributed data).

2004]. However, neither the perception of fatigue nor the impact of fatigue was associated with classical systemic inflammatory markers such as IL-6 and CRP in patients with COPD. The absence of a relationship is in agreement with earlier studies [Baghai-Ravary *et al.* 2008; Lewko *et al.* 2009]. Al-Shair and colleagues reported a modest correlation between markers of systemic inflammation and fatigue intensity assessed with a Borg scale before and after a 6MWD test. However, no statistically significant correlation between different dimensions of fatigue and systemic biomarkers was demonstrated [Al-Shair *et al.* 2011]. Furthermore, neither Baghai-Ravary and colleagues nor Lewko and colleagues found any evidence for a relationship between fatigue in patients with stable COPD and CRP levels and IL-6, respectively [Baghai-Ravary *et al.* 2008;

Table 4. Potential factors associated ($p < 0.200$) with physiological, psychosocial and cognitive dimension of Fatigue Impact Scale (FIS) ($n = 73$).

Potential factors	FIS physical (0–40)		FIS psychosocial (0–80)		FIS cognitive (0–40)	
Situational						
Age, y	$r = -0.02$		$r = -0.16$[a]		$r = -0.17$[a]	
Current smoking Yes = 18 No = 55	Md 24.5 Md 18.0	$p = 0.16$	Md 32.5 Md 23.0	$p = 0.29$	 Md 17.0 Md 8.0	$p = 0.01$
*Pack-years	$r = 0.15$		$r = 0.16$[a]		$r = 0.17$[a]	
Physiological						
FEV1% predicted	$r = -0.16$[a]		$r = -0.17$[a]		$r = 0.13$	
6MWD	$r = -0.27$*		$r = -0.28$*		$r = 0.04$	
mMRC dyspnoea mMRC⩽1 = 22 mMRC⩾2 = 51	Md 14.0 Md 23.0	$p = 0.004$	Md 20.5 Md 30.0	$p = 0.10$	Md 15.5 Md 9.0	$p = 0.24$
Surfactant protein D ($n = 71$)	$r = 0.16$[a]		$r = 0.17$[a]		$r = 0.10$	
Psychological						
HADS anxiety	$r = 0.38$**		$r = 0.50$**		$r = 0.43$**	
HADS depression	$r = 0.52$**		$r = 0.61$**		$r = 0.50$**	
MISS insomnia	$r = 0.14$		$r = 0.18$[a]		$r = 0.27$*	

[a]$p < 0.20$ *$p < 0.05$; **$p < 0.01$. 6MWD, six-minute walk distance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1 % predicted, forced expiratory volume over 1 second of predicted; HADS, Hospital Anxiety and Depression scale; MISS, Minimal Insomnia Symptom scale; mMRC, modified Medical Research Council dyspnoea scale. *Pack-year, number of years smoking × average number of cigarettes smoked per day /20.

Lewko *et al.* 2009]. Altogether, these results suggest that systemic inflammation may be of marginal significance as a predictor for fatigue in patients with stable COPD. However, in this study, a weak but significant and consistent association between SP-D and two dimensions of impact of fatigue was demonstrated. Sin and colleagues reported an association between circulating SP-D and dyspnoea, and as circulating SP-D levels increased, patients experienced an increase in dyspnoea and a worsening of their health status [Sin *et al.* 2007]. SP-D could have the potential to serve as a biomarker that is associated with subjective variables such as dyspnoea and possibly also fatigue. It is possible that our findings could indicate a link between the impact of fatigue and an inflammatory process taking place in the lungs, although the relationship was weak and our results demand further analysis.

Psychological factors

In addition to physiological explanations for experience of fatigue, psychological factors should be taken into account. In the present study, depressive symptoms were associated with experience of fatigue, and similar findings have been previously reported [Breslin *et al.* 1998; Kapella *et al.* 2006; Lewko *et al.* 2009]. Anxiety and depression symptoms are common in patients with COPD [Maurer *et al.* 2008] and may be underdiagnosed [Barnes and Celli, 2009]. One important finding in this study was that almost all patients with clinically-relevant depressive and anxiety symptoms experienced fatigue. These results show that it is important to ask patients if they have perceived fatigue in order to reveal clinically relevant depression. Depressive symptoms were also common predictors for all dimensions of the impact of fatigue, and these findings are in line with Lewko and colleagues [Lewko *et al.* 2009].

Next to depressive symptoms, having sleep problems was revealed as a predictor of experience fatigue. Sleep problems, consisting of difficulty falling asleep and staying asleep, were significantly more pronounced in patients with fatigue. Moreover, it has been reported that 50% of patients with COPD have difficulty falling asleep and staying asleep or have unrefreshing sleep [Bellia *et al.* 2003]. Our result emphasizes, in line with data from Kapella and colleagues, the need to focus on treatment of insomnia problems [Kapella *et al.* 2011].

Table 5. Multiple linear regression (backward) of the situational, physiological and psychological factors on functional limitation due to fatigue in patients with stable COPD ($n = 73$).

Variable	Functional limitation due to fatigue assessed with Fatigue Impact Scale (FIS)													
	Physical dimension of FIS					Psychosocial dimension of FIS					Cognitive dimension of FIS			
	B	SE	β	t	*p*-value	B	SE	β	t	*p*-value	B	SE	β	t	*p*-value
Situational														
Age						−0.415	0.244	−0.183	−1.700	0.094				
Current smoking											4.468	2.019	0.223	2.213	0.030
Physiological														
SP-D	0.045	0.020	0.221	2.215	0.030	0.092	0.036	0.241	2.557	0.013				
6MWD						−0.024	0.013	−0.190	−1.794	0.078				
mMRC Dyspnoea	4.674	2.046	0.229	2.284	0.026									
Psychological														
Depression score	1.283	0.267	0.486	4.809	<0.001	1.992	0.591	0.403	3.368	0.001	0.981	0.231	0.430	4.255	<0.001
Anxiety score						0.839	0.456	0.225	1.840	0.070					
Insomnia score											0.521	0.309	0.169	1.689	0.096
Constant	3.96	2.98				38.53	20.70				0.596	2.55			
R2	0.348					0.475					0.332				
VIF	<1.05					<1.90					<1.06				

β, standardized regression coefficient (beta); 6MWD, six-minute walk distance; mMRC, modified Medical Research Council dyspnoea scale (dichotomized as no dyspnoea, ⩽ 1 score, and dyspnoea, ⩾2 scores on MRC); R^2, explanatory power; SP-D, surfactant protein D; VIF, variance inflation factor.

Situational factors

The experience of fatigue among patients with COPD was mainly associated with physiological and psychological factors. There were no clear associations with situational factors such as age or gender, and despite a slight difference in education level between the patients with and without fatigue, the regression analyses were negative. These findings contrast with Kapella and colleagues, who reported that fatigue was significantly correlated with age [Kapella *et al.* 2006]. However, the results are in line with Oh and colleagues, Theander and colleagues and Gift and Shepherd who reported that men and women did not differ in level of fatigue [Oh *et al.* 2004; Theander *et al.* 2011; Gift and Shepherd, 1999]. The only significant finding regarding situational factors and impact of fatigue was a relation between current smoking and cognitive dimension.

Strength and limitations

The use of standardized questionnaires and objective measures that allow comparisons with other studies could be considered a main strength of the study. FIS is a multidimensional instrument which identifies the impact of fatigue on patients with COPD [Fisk *et al.* 1994], and is seen as the most relevant instrument for assessing the impact of fatigue. Furthermore, to explore fatigue and the impact of fatigue in a model, using the conceptual framework middle-range theory of unpleasant symptoms [Lenz *et al.* 1997] with all of these influencing factors included, enables a broader concept to study COPD-related fatigue.

However, the variance of the impact of fatigue is not fully explained and there are factors not included in the study that may potentially contribute, such as the prevalence of anaemia, undetected sleep apnoea syndrome, comorbidities and medication. In addition, the selection of patients may lead to difficulty in the generalization of our findings to all patients with COPD. The patients in this study were recruited from two outpatient clinics in hospitals, which may increase the risk of a selection bias with more comorbidities than in a primary outpatient clinic. Therefore, we excluded the patients with diseases that had a potentially confounding effect on influencing factors for experience of fatigue. Moreover, almost 80% of the patients in this study had stage II and III COPD, suggesting that these results cannot be generalized to patients with mild or very severe COPD. We also did not take account of the differences that may exist with different treatment modalities.

Clinical implications

This study confirms that fatigue is a more burdensome symptom in patients with COPD than in control patients with same age and gender. In agreement with earlier studies [Antoniu *et al.* 2016], presence of clinically significant fatigue in patients with COPD is associated with worse health status. Patients with COPD, seem to suffer fatigue which is more pronounced, has longer duration, and is associated with a greater impact on daily life. In addition, almost all patients with clinically relevant depressive and anxiety symptoms experienced fatigue. These facts emphasize the importance of understanding the underlying mechanism for minimizing the burden of fatigue. Moreover, the presence of dyspnoea, depressive symptoms and insomnia problems should be noted and treated in order to reduce fatigue. Although the study revealed several factors related to the impact of fatigue in COPD, much of the variance remained unexplained. Therefore, future studies should focus on identifying these predictors.

Conclusion

This study demonstrates that fatigue is a common and important symptom in patients with COPD. The experiences of fatigue and functional limitation due to fatigue seem to be related mainly to a combination of physiological and psychological influencing factors, with dyspnoea, depressive symptoms and insomnia problems as the most prominent factors associated with the perception as well as the impact of fatigue. Systemic inflammation was not associated with perception of fatigue but SP-D was connected to some dimensions of the impact of fatigue. Overall, it seems that there are stronger associations between fatigue and psychological variables than between fatigue and physiological parameters in patients with stable COPD.

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Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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