



Perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis

Ada E. M. Bloem^{1,2}, Rémy L. M. Mostard³, Naomi Stoot³, Jan H. Vercoulen⁴, Jeannette B. Peters⁵, Martijn A. Spruit^{6,7}

¹University of Applied Sciences Utrecht, Institute of Movement Studies, Faculty of Health Care, Utrecht, The Netherlands; ²ILD Centre of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, The Netherlands; ³Department of Respiratory Medicine, Zuyderland Medical Center Heerlen, Heerlen/Sittard-Geleen, The Netherlands; ⁴Department of Medical Psychology, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands; ⁵Department of Pulmonary Diseases, Radboud University Medical Center, Radboud Institute for Health Sciences, Nijmegen, The Netherlands; ⁶Department of Research and Development, CIRO, Horn, The Netherlands; ⁷Department of Respiratory Medicine, Maastricht University Medical Center, NUTRIM School of Nutrition and Translational Research in Metabolism, Faculty of Health, Medicine and Life Science, Maastricht, The Netherlands

Contributions: (I) Conception and design: AEM Bloem, RLM Mostard, JH Vercoulen, MA Spruit; (II) Administrative support: AEM Bloem, N Stoot; (III) Provision of study materials or patients: RLM Mostard, N Stoot; (IV) Collection and assembly of data: AEM Bloem; (V) Data analysis and interpretation: AEM Bloem, RLM Mostard, JH Vercoulen, JB Peters, MA Spruit; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ada E. M. Bloem, Heidelberglaan 7, 3584 CS, Utrecht, The Netherlands. Email: aadje.bloem@hu.nl.

Background: Fatigue is highly prevalent in patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis. However, the difference in fatigue perceptions for these patients is unknown and this may be important to better understand what fatigue means to the individual patient.

Methods: This cross-sectional quantitative study aims to determine the different perceptions of fatigue as 'frustrating', 'exhausting', 'pleasant', 'frightening' using the Fatigue Quality List and to assess determinants related to these perceptions of fatigue. Beside the fatigue quality connotations, demographics, lung function, fatigue severity (Checklist Individual Strength subscale Fatigue), dyspnea (modified-Medical Research Council), fatigue catastrophizing (Fatigue Catastrophizing Scale), anxiety/depression (Hospital Anxiety and Depression Scale) and general health status (EuroQoL 5-dimension 5-level) were assessed.

Results: Mean frequency score of fatigue-related perceptions in patients with IPF was 3.4 points and in patients with sarcoidosis 4.0 points. Severely fatigued patients with IPF reported their fatigue less 'pleasant' significantly more often than patients without severe fatigue. Fatigue severity, dyspnea, catastrophizing and general health were significantly correlated with the negative connotation categories of the Fatigue Quality List in patients with IPF. Severely fatigued sarcoidosis patients reported their fatigue perceptions significantly more often as 'frustrating', 'exhausting', 'frightening' and less 'pleasant' than patients without severe fatigue. Moreover, in patients with sarcoidosis fatigue severity, dyspnea, catastrophizing and depression were significantly associated with all four categories of the Fatigue Quality List that describe the experienced fatigue ($P < 0.05$).

Conclusions: The current findings of experiences of fatigue in patients with IPF or pulmonary sarcoidosis provide insights for professionals treating these patients. Although similarities were found in the several experiences of fatigue across non-severely and severely fatigued patients, differences were also evident and could be mapped for IPF and sarcoidosis.

Keywords: Idiopathic pulmonary fibrosis (IPF); sarcoidosis; fatigue; perceptions

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Introduction

Idiopathic pulmonary fibrosis (IPF) and sarcoidosis are diseases belonging to the interstitial lung diseases (ILDs). ILDs comprise a large group of respiratory disorders affecting the interstitium of the lungs (1,2). Although ILDs include diseases with different pathophysiology and prognostics, most patients with ILD experience similar symptoms as shortness of breath, fatigue, dry cough and impaired exercise tolerance. It is known that fatigue is highly prevalent in patients with idiopathic pulmonary fibrosis (IPF) or sarcoidosis (1-6). To date, no data are available about the different perceptions of fatigue in these patients. This, however, may be important to create a better understanding of what fatigue means to the individual patient, and to determine whether or not it is a possible target for intervention.

The perception of fatigue can differ between individuals. For example, healthy individuals use adjectives such as normal, pleasant, relaxing, fulfilling and temporary to describe fatigue (7). Contrary, patients with different chronic conditions (i.e., chronic fatigue syndrome, neuromuscular diseases, pancreatitis, post-cancer fatigue, rheumatoid arthritis and chronic obstructive pulmonary disease) more often use negative adjectives such as frustrating, exhausting, upsetting and frightening (7-9).

The degree of fatigue severity may, at least partially, influence the perception of fatigue. Indeed, patients with severe fatigue describe their fatigue more often as frustrating or exhausting, whereas non-severely fatigued patients perceived their fatigue as normal (7,8). Additionally, symptoms of breathlessness, anxiety/depression and catastrophic thoughts of fatigue may also have contributed to the different experiences of fatigue (9,10). IPF and sarcoidosis are two different chronic pulmonary diseases in pathophysiological perspective, in which IPF is a fatal disease with progressive fibrosing of the lung with only some delay by antifibrotic medication and sarcoidosis is characterized by granulomatous inflammation with possible immunosuppressant therapy (1,2). Severe fatigue was present 48% of patients with IPF and 69% in patients with sarcoidosis, but the differences in perceptions remained unclear.

To find out more about the perceptions of fatigue in patients with IPF or sarcoidosis, the aims of this study were: (I) to assess the different perceptions of fatigue in IPF or pulmonary sarcoidosis; (II) to evaluate the association

between the different perceptions of fatigue and clinical parameters; and (III) to assess determinants related to general health.

We present the following article in accordance with the SURGE reporting checklist (available at <https://dx.doi.org/10.21037/jtd-21-462>).

Methods

Study design and participants

In the period between May 2018 and March 2019, patients (age ≥ 18 years) with a confirmed diagnosis of IPF (2,11) or pulmonary sarcoidosis (12,13) were invited to participate in this cross-sectional clinical fatigue study (6). The study setting was at the outpatient clinic of the Department of Respiratory Medicine, Zuyderland Medical Centre Heerlen (The Netherlands). Patients were excluded if one of the following issues occurred: insufficient understanding of the Dutch language and/or inability to complete questionnaires due to cognitive impairment, or simultaneous participation in a potentially conflicting intervention study. Before this study (no funding) started, Medical Ethical Committee approval was granted (METCZ20180027) and registration with the Netherlands Trial Register (Code 7201) was established. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The study protocol was in short: The chest physician (RM) invited eligible patients during the regular outpatient visit to participate in the study and he provided them with the written explanation. After that, patients met the nurse practitioner (NS) for complementary information of study participation and, if partaking, written informed consent; All participations were given a unique code (NS). Study participation involved completing the paper-and-pencil questionnaires directly or at home after a reflection period; The one-time participation was on a voluntary basis. Data were collected from medical records (NS) to provide information on: age (years), gender (man/woman), diagnosis, comorbidities, smoking pack-years (average packs smoked per day \times duration of smoking, in years), medication, last available (within the preceding three months) spirometry (forced vital capacity, forced expiratory volume in one second; Liter, % predicted), static lung volumes (total lung capacity, residual volume; Liter, % predicted), and diffusing capacity for carbon

monoxide (TLCO; % predicted) (14).

Measures

Experiences of fatigue

The primary outcome measure was the difference in the experiences of fatigue. For the multidimensional perceptions of fatigue inventory the Fatigue Quality List (FQL) was used. The short form FQL consists of single choice questions (yes/no) for 18 adjectives (FQL-Adjectives) belonging to one of the FQL-categories ‘frustrating’, ‘exhausting’, ‘pleasant’ or ‘frightening’. Patients were instructed to indicate which of the adjectives suited their experienced fatigue; multiple answers were allowed (7). Then the adjectives were divided into one of four fatigue description categories (FQL-Categories) with a score range of 0–100 points within each category. Adjectives belonging to the category frustrating (FQL-Frustrating) are discouraging, incessant, annoying, persistent and frustrating. Adjectives belonging to the category exhausting (FQL-Exhausting) are exhausting, wearisome, extreme and unbearable. In the category pleasant (FQL-Pleasant) are temporary, relaxing, fulfilling, normal and pleasant. And in the category frightening (FQL-Frightening) are upsetting, frightening, inexplicable and insuperable (7).

Demographic characteristics

Participants self-reported the following demographic data on partner (yes/no), living situation (alone/cohabiting), education (“low education level” meaning maximally preparatory school and “high education level” meaning minimally secondary vocational education), height (m), weight (kg), hospitalization last year (yes/no), working situation last 2 years (yes/no), psychological support (yes/no) and smoking (former/current, never).

Self-reported questionnaires

Fatigue severity was assessed by the Checklist Individual Strength subscale fatigue (CIS-Fatigue). The subscale CIS-Fatigue (eight items) investigates the patients’ severity of fatigue of the previous two weeks (15,16). Each item was scored on a seven-point Likert scale with a total item score range of 8–56 points. A score of points ≤ 26 indicates normal fatigue, between 27–35 moderate fatigue (called together non-severe fatigue < 36 points), and a score of ≥ 36 indicates severe fatigue (17,18).

Activity-related dyspnea was measured with the modified medical research council scale for dyspnea

(mMRC). The severity of dyspnea is indicated on a 5-point scale (0–4 score; higher level reflects more activity limitation due to dyspnea) (19).

To investigate catastrophizing thoughts related to fatigue the Fatigue Catastrophizing Scale (FCS) was used. The FCS was adapted from the pain catastrophizing scale (PCS) by replacing the term “pain” with “fatigue” where relevant (20). This scale consists of 13 items measuring the relation of catastrophizing to fatigue on a 5-point scale from 0 (not at all) to 4 (always), with a total maximum of 52 points. Higher scores are indicative for more fatigue catastrophizing (21).

The Hospital Anxiety and Depression Scale (HADS) is a self-reporting instrument to estimate emotional distress, consisting of two subscales for anxiety (HADS-Anxiety) and depression (HADS-Depression) in somatically ill patients (22,23). Total scores for each subscale range from 0 to 21 points, categorized as: normal/mild (0–10 points) and moderate/severe (11–21 points, meaning a clinically significant case of anxiety or depression) (22).

The patients’ self-rated general health (score of today) was recorded with the visual analog scale of the European Quality of Life-5 Dimensions (EQ-5D-5L VAS) and the 5-dimension list (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) (24). The vertically situated VAS had labelled endpoints from 0 (worst imaginable health) to 100 points (best imaginable health). The 5-dimension list results were converted into an index value (EQ-5D-5L index value) (25).

Statistical analyses

Data were presented with appropriate measures of central tendency and dispersion, as mean \pm standard deviation (SD), median and interquartile range, or frequencies and proportions. Numerical data were tested for normality by Shapiro-Wilkinson test, a mean-median ratio, SD-mean ratio, and judging the histogram (26). Differences between groups for continuous data were analyzed by an unpaired *t*-test or the non-parametric pendant (Mann–Whitney U test) where appropriate. Categorical data were analyzed with the Chi-square or Fisher Exact test. A P value of ≤ 0.05 was considered as statistically significant. Univariate differences between non-severely (mild/moderate fatigue) and severely fatigued patients were tested with independent *t*-tests, Mann–Whitney U-tests and chi-square-tests were performed as appropriate. Pearson’s *r* or Spearman’s ρ were used to study correlations between the continuous data FQL-Categories or EQ-5D-5L (VAS or index value)

and patient characteristics or psychosocial factors. In case of missing values, cases were excluded pairwise. The range for what constitutes a weak, moderately strong, strong, or very strong correlation was respectively $0.1 \leq r < 0.3$, $0.3 \leq r < 0.5$, $0.5 \leq r < 0.7$, and $0.7 \leq r < 1.0$ [45,46] (level of significance $P < 0.05$). Stepwise multiple linear regression with backward selection procedure was performed to investigate the associations between the EQ-5D-5L VAS or EQ-5D-5L index value and independent in univariate analysis significant variables ($P < 0.05$). In case of multicollinearity, variables were identified [variance inflation factor (VIF) > 5] and removed from the model (27). IBM SPSS Statistics (Version 25) was used for statistical analysis.

Results

General characteristics

Of the 170 patients invited to participate in this fatigue study, 61 patients with IPF responded (92% response rate) and 60 patients with sarcoidosis (58% response rate). General characteristics of the patients with IPF or sarcoidosis are shown in *Table 1*. Most patients with IPF were elderly men, with a low education level, a smoking history and a slightly increased body mass index (BMI). They had an impaired lung function, most of these patients were diagnosed with one or more comorbidities, and 87% used anti-fibrotic medication. Severe fatigue was prevalent in 48% of the patients with IPF and 51% had more severe scores on activity-related dyspnea (mMRC ≥ 2). Moreover, moderate/severe anxiety or depression was present in 9% of the patients with IPF, patients had a mild degree of catastrophic thoughts related to fatigue, and 52% scored VAS general health at 60 points or less (data not shown).

The patients with sarcoidosis were middle aged and had an increased mean BMI. Patients mainly used medication such as immuno-suppressants (39%) and divers medication for lung conditions (56%). 69% of patients with sarcoidosis were severely fatigued and 36% were more impaired in walking due to dyspnea (mMRC ≥ 2). Also, moderate/severe anxiety and depression was reported by 12% and 8% of the patients with sarcoidosis. They had a mildly elevated score of catastrophizing, and 46% self-rated general health at 60 points or less (data not shown).

Perceptions of fatigue in patients with IPF

Patients were allowed to report as many adjectives for

fatigue as they found appropriate. In patients with IPF the mean score was 3.4 adjectives (3.2 SD). The distribution of the frequency of adjectives is depicted in *Figure 1A*. The mean number of adjectives was similar between IPF patients with or without severe fatigue (4 versus 3 respectively, $P > 0.05$). IPF patients with severe fatigue reported significantly more adjectives as upsetting, incessant, wearisome and persistent than the non-fatigued patients. Not one patient stated fatigue as normal. With respect to the categories of the FQL, severely fatigued patients with IPF only scored significantly less on FQL-Pleasant than non-severe fatigued patients (*Table 2*).

Perceptions of fatigue in patients with sarcoidosis

The mean of the sum of adjectives reported by patients with sarcoidosis was 4.0 (3.0 SD). Severely fatigued patients with sarcoidosis used a higher number of adjectives to describe their experience of fatigue than the non-severe fatigued patients: 5 versus 2 adjectives, respectively ($P < 0.05$; *Table 3*, *Figure 1B*). The severely fatigued patients more often reported the following adjectives of fatigue: discouraging, temporary, exhausting, incessant, wearisome, annoying, extreme, persistent, frustrating, inexplicable and normal (*Table 3*). With respect to the categories of the FQL, patients with severe fatigue significantly scored higher on FQL-Frustrating, FQL-Exhausting and FQL-Frightening, and significantly less on the FQL-Pleasant than patients with non-severe fatigue ($P < 0.05$; *Table 2*).

Perceptions of fatigue in patients with IPF or sarcoidosis with severe fatigue

Severely fatigued patients with IPF or sarcoidosis generally used the same percentage of adjectives to express their fatigue experience. However, the adjectives exhausting and frustrating were reported by a significant higher number of severely fatigued patients with sarcoidosis as compared to severely fatigued patients with IPF. Moreover, there were no significant differences between both groups with respect to the categories FQL-Frustrating, FQL-Exhausting, FQL-Pleasant and FQL-Frightening, and the highest scores were seen in the category FQL-Frustrating in both patient groups (IPF 34 points, sarcoidosis 48 points).

Univariate correlations of perceptions of fatigue

Table 4 gives an overview of all significant correlations

Table 1 General characteristics of patients with interstitial lung disease, idiopathic pulmonary fibrosis (IPF) or sarcoidosis

Variables	Patients with IPF (n=61)	Patients with Sarcoidosis (n=60)
General Characteristics		
Gender, male, n (%)	47 (77.0)	29 (48.3)
Age, years [IQR]	73.0 [70–78]	53.5 [46.3–62.0]
Partner, n (%)	45 (73.8)	44 (73.3)
Living together, n (%)	41 (67.2)	42 (70.0)
Education, low <secondary level, n (%) ^p	30 (50.8)	13 (21.7)
Diagnosis time, ≤1 year, n (%) ^b	21 (35.0)	16 (27.1)
Hospitalization, ≤1 year, n (%) ^a	14 (23.0)	10 (16.9)
Work, last 2 years, n (%)	12 (19.7)	37 (61.7)
Psychological support, n (%)	9 (14.8)	20 (33.3)
Smoking, current/former, n (%) ^a	48 (78.7)	23 (39.0)
Pack-years ⁺ , smoking current/former ⁱ	19.5±19.4	10.6±13.9
Physiological		
BMI (kg/m ²) ^a	27.5±4.1	27.6±4.2
TLC (liter) ^h	4.6±1.1	6.0±1.3
TLC (% predicted) ⁱ	73.3±14.1	98.5±18.5
RV (liter) ^g	1.6±0.4	2.0±0.5
RV (% predicted) ⁱ	64.8±14.2	97.9±25.7
FVC (liter)	2.9±0.8	3.9±1.1
FVC (% predicted)	82.8±19.4	98.1±20.8
FEV ₁ (liter)	2.3±0.6	2.9±0.9
FEV ₁ (% predicted)	87.0±20.7	91.5±20.3
TLCO (liter) ^e	3.8±1.3	7.3±2.0
TLCO (% predicted) ^e	48.7±15.2	81.6±18.3
Comorbidity ≤1, n (%) ^b	45 (75)	30 (51)
Medication		
IPF - antifibrotic, n (%)	53 (86.9)	0 (0.0)
Immunosuppressant incl. prednisone (corticosteroids), n (%) ^c	5 (8.5)	23 (39.0)
Heart rate-lowering medication, n (%) ^c	16 (27.1)	7 (11.9)
Antidepressant medication, n (%) ^c	5 (8.5)	1 (1.7)
Antihypertensive medication, n (%) ^c	26 (44.1)	11 (18.6)
Medication for pulmonary conditions, n (%) ^c	7 (11.9)	33 (55.9)
Fatigue		
CIS-Fatigue ¹ (p, 8–56) ^d	34.1±11.2	40.0±12.3
CIS, Severe >35 points, n (%) ^d	28 (47.5)	40 (69.0)

Table 1 (continued)

Table 1 (continued)

Variables	Patients with IPF (n=61)	Patients with sarcoidosis (n=60)
Dyspnea		
mMRC ² (p, 0–4) ^g	1.9±1.2	1.4±1.1
Fatigue catastrophizing		
FCS ³ (p, 0–52) ^f	14.7±13.4	13.1±11.2
Anxiety and depression		
HADS-Anxiety ⁴ (p, 0–21) ^e	5.4±3.8	5.1±3.7
HADS-Anxiety, ≥11 points (n, %)	5 (8.8)	7 (11.9)
HADS-Depression ⁴ (p, 0–21) ^c	5.0±3.3	4.7±3.7
HADS-Depression, ≥11 points (n, %)	5 (8.6)	5 (8.3)
Quality of life, general health		
EQ-5D-5L VAS ⁵ (p, 0–100) ^b	63.8±16.6	62.7±19.6
EQ-5D-5L index value ⁶ (p, 0–1) ^b	0.7±0.2	0.7±0.2

Data are presented as mean ± SD, median [IQR] or n (%). * Pack-year, number of years smoking x average number of cigarettes smoked per day/20. Alphabetic characters in superscript indicates a sample size deviant from n=121, in the order: ^a n=120, ^b n=119, ^c n=118, ^d n=117, ^e n=116, ^f n=115, ^g n=114, ^h n=113, ⁱ n=112, ^j n=52. ¹, CIS-Fatigue scores range from 8 to 56; high scores indicate more fatigue; ², mMRC score range from 0 to 4; high scores indicate more activity related dyspnea; ³, FCS score range from 0 to 52; high scores indicate more catastrophizing of fatigue; ⁴, HADS-Anxiety or ⁴HADS-Depression score range from 0 to 21; high scores indicate more experience of anxiety or depression; ⁵, EQ-5D-5L VAS score range from 0 to 100; high score indicate better general health (today); ⁶, EQ-5D-5L index value score range from 0 to 1; score 1 mean full health. BMI, body mass index; CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L, EuroQol, 5 dimensions, 5 levels (standardised measure of health status); FCS, Fatigue Catastrophizing Scale; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HADS-Anxiety: hospital anxiety and depression scale subscale anxiety; HADS-Depression: hospital anxiety and depression scale subscale depression; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; mMRC, modified Medical Research Council dyspnea scale; p, points; RV, residual volume; RV/TLC, residual volume to total lung capacity; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; VAS, Visual Analog Scale.

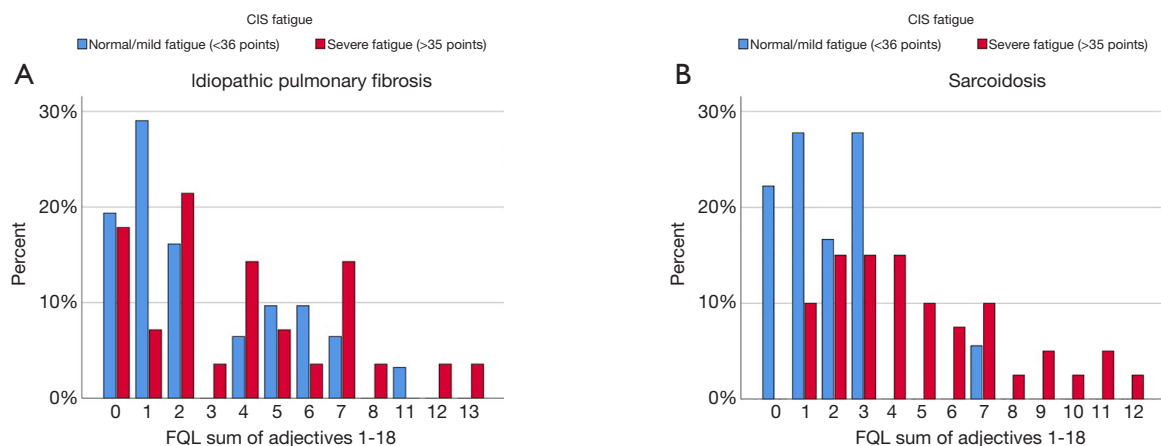


Figure 1 Frequency of adjectives for fatigue stratified for fatigue severity in patients with idiopathic pulmonary fibrosis or sarcoidosis. (A) Frequency of adjectives for fatigue stratified for fatigue severity in patients with idiopathic pulmonary fibrosis; (B) frequency of adjectives for fatigue stratified for fatigue severity in patients with sarcoidosis. CIS Fatigue, Checklist Individual Strength subscale Fatigue; FQL, Fatigue Quality List.

Table 2 Categories perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis, stratified for fatigue severity

Categories	Fatigue severity in patients with IPF				Sarcoidosis (n=60)	Fatigue severity in patients with sarcoidosis			IPF-sarcoidosis, severe fatigue P value
	IPF (n=61)	Non-severe fatigue (n=31)	Severe fatigue (n=28)	P value		Non-severe fatigue (n=18)	Severe fatigue (N=40)	P value	
Frustrating (p, 0–100)	26.2±30.9	18.1±24.4	33.6±34.9	NS	36.3±32.6	7.8±14.0	48±30.0	<0.05	NS
Exhausting (p, 0–100)	17.6±27.5	10.5±21.2	23.2±28.8	NS	22.5±29.0	4.2±12.9	31.3±30.9	<0.05	NS
Pleasant (p, 0–100)	12.1±19.4	17.4±24.1	7.1±11.2	<0.05	10.7±15.4	20.0±18.2	7.0±12.4	<0.05	NS
Frightening (p, 0–100)	18.4±28.1	13.7±27.3	24.1±29.3	NS	17.5±25.3	6.9±18.8	21.3±26.9	<0.05	NS

Data are presented as mean ± SD; P value (Student's *t*-test) in bold indicates a significant difference <0.05; Fatigue severity is based on the Checklist Individual Strength subscale Fatigue (CIS-Fatigue): 'Non-severe Fatigue' CIS-Fat <36 points, 'Severe Fatigue' CIS-Fat ≥36 points. In case of missing data of CIS-Fatigue cases were excluded analysis by analysis. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; IPF, idiopathic pulmonary fibrosis; NS, not significant; p, points. FQL scores range from 0 to 100; higher scores in each category indicate fatigue is frustrating, exhausting, pleasant, or frightening to a higher degree.

($P < 0.05$) between the four FQL-Categories and fatigue severity (CIS-Fatigue), dyspnea (mMRC), fatigue catastrophizing (FCS), anxiety (HADS-Anxiety), depression (HADS-Depression) and general health status (EQ-5D-5L VAS). In patients with IPF catastrophizing fatigue correlated strongly ($0.5 \leq \rho < 0.7$) with the three categories of the FQL representing negative adjectives and not one of these concepts correlated with the experience of pleasant fatigue. In patients with sarcoidosis strong correlations were found between FQL-Frustrating and fatigue severity, catastrophizing, depression and general health, and in FQL-Exhausting the same traits supplemented with dyspnea and anxiety. FQL-Pleasant was strongly correlated with general health and FQL-Frightening with catastrophizing (Table 4).

Determinants of general health

Table 5 shows the associations for general health (EQ-5D-5L VAS and EQ-5D-5L index value) with fatigue severity (CIS-Fatigue), experience of fatigue (FQL-categories) and other clinical parameters. In patients with IPF moderately strong correlations with general health (EQ-5D-5L VAS or index value) were found with the FQL-Frustrating, FQL-Exhausting and FQL-Frightening, but no significant correlation with FQL-Pleasant. In patients with sarcoidosis general health (EQ-5D-5L VAS or index value) showed strong correlations with FQL-frustrating, FQL-Exhausting

and FQL-Pleasant, and moderately strong correlation of the EQ-5D-5L index value with FQL-Frightening. The regression equations with the dependent variables EQ-5D-5L VAS or index value are presented in Table 6. The explained variance (R^2) of the stepwise multiple regression models for patients with IPF vs. sarcoidosis was for EQ-5D-5L VAS 58% vs. 59% and for EQ-5D-5L index value 75% vs. 56%.

Discussion

This study shows that there are extensive variations in perceptions of fatigue in patients with IPF or sarcoidosis, in addition to the severity of fatigue. Patients expressed their perceived fatigue in a different number of adjectives, ranging from 0 to 13 adjectives. Also, severely fatigued patients with IPF perceived their fatigue (categories FQL) less as pleasant than non-severely fatigued IPF patients. Severely fatigued patients with sarcoidosis perceived their fatigue as more frustrating, exhausting, frightening and less pleasant compared to non-severely fatigued patients. Although a third of the patients without severe fatigue reported their fatigue as normal and temporary, some of these non-severely fatigued patients also had negative associations with fatigue, such as exhausting (14%), frightening (14%), annoying (18%) and frustrating (29%). The findings in this study for negative connotations of fatigue are in line with other chronic diseases (7-9).

Table 3 Perceptions of fatigue in patients with idiopathic pulmonary fibrosis or sarcoidosis, stratified for fatigue severity

Fatigue Quality List	IPF (n=61)	Fatigue severity in patients with IPF			Sarcoidosis (n=60)	Fatigue severity in patients with sarcoidosis			IPF – sarcoidosis, severe fatigue
		Non-severe fatigue (n=31)	Severe fatigue (n=28)	P value		Non-severe fatigue (n=18)	Severe fatigue (N=40)	P value	
Upsetting, n (%)	14 (23.0)	4 (12.9)	10 (35.7)	<0.05*	11 (18.3)	2 (11.1)	9 (22.5)	NS**	NS*
Discouraging, n (%)	13 (21.3)	4 (12.9)	8 (28.6)	NS*	15 (25.0)	1 (5.6)	13 (32.5)	<0.05**	NS*
Temporary, n (%)	16 (26.2)	10 (32.3)	6 (21.4)	NS*	18 (30.0)	9 (50.0)	9 (22.5)	<0.05*	NS*
Exhausting, n (%)	15 (24.6)	6 (19.4)	8 (28.6)	NS*	22 (36.7)	1 (5.6)	21 (52.5)	<0.05*	NS (P=0.05)*
Incessant, n (%)	12 (19.7)	3 (9.7)	9 (32.1)	<0.05*	20 (33.3)	1 (5.6)	18 (45.0)	<0.05*	NS*
Wearisome, n (%)	17 (27.9)	4 (12.9)	12 (42.9)	<0.05*	15 (25.0)	1 (5.6)	14 (35.0)	<0.05**	NS*
Frightening, n (%)	11 (18.0)	6 (19.4)	5 (17.9)	NS*	8 (13.3)	1 (5.6)	6 (15.0)	NS**	NS**
Annoying, n (%)	20 (32.8)	8 (25.8)	11 (39.3)	NS*	20 (33.3)	1 (5.6)	18 (45.0)	<0.05*	NS*
Extreme, n (%)	7 (11.5)	2 (6.5)	4 (14.3)	NS**	10 (16.7)	0 (0.0)	10 (25.0)	<0.05**	NS*
Persistent, n (%)	11 (18.0)	2 (6.5)	8 (28.6)	<0.05**	21 (35.0)	1 (5.6)	19 (47.5)	<0.05*	NS*
Frustrating, n (%)	24 (39.3)	11 (35.5)	11 (39.3)	NS*	33 (55.0)	3 (16.7)	28 (70.0)	<0.05*	<0.05*
Relaxing, n (%)	5 (8.2)	2 (6.5)	3 (10.7)	NS**	1 (1.7)	0 (0.0)	1 (2.5)	NS**	NS**
Inexplicable, n (%)	10 (16.4)	3 (9.7)	6 (21.4)	NS**	15 (25.0)	1 (5.6)	13 (32.5)	<0.05*	NS*
Fulfilling, n (%)	2 (3.3)	2 (6.5)	0 (0.0)	NS**	3 (5.0)	2 (11.1)	1 (2.5)	NS**	NS**
Insurmountable, n (%)	10 (16.4)	4 (12.9)	6 (21.4)	NS**	8 (13.3)	1 (5.6)	6 (15.0)	NS**	NS*
Unbearable, n (%)	4 (6.6)	1 (3.2)	2 (7.1)	NS**	7 (11.7)	1 (5.6)	5 (12.5)	NS**	NS**
Normal, n (%)	9 (14.8)	9 (29.0)	0 (0.0)	<0.05**	10 (16.7)	7 (38.9)	3 (7.5)	<0.05*	NS**
Pleasant, n (%)	5 (8.2)	4 (12.9)	1 (3.6)	NS**	0 (0.0)	0 (0.0)	0 (0.0)	NS**	NS**
Total descriptions, (p, 0–18)	3.4±3.2	2.7±2.8	3.9±3.5	NS [~]	4.0±3.0	1.8±1.7	4.9±3.0	<0.05 [#]	NS [~]

Data are presented as n (%) or mean ± SD, P value in bold indicates a significant difference <0.05. *, Pearson Chi-Square test; **, Fisher's Exact Test; #, Student's T-test. Fatigue severity is based on the Checklist Individual Strength subscale Fatigue: 'Non-severe Fatigue' CIS-Fatigue <36 points, 'Severe Fatigue' CIS-Fatigue ≥36 points. In case of missing data of CIS-Fatigue cases were excluded analysis by analysis. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; IPF, idiopathic pulmonary fibrosis; ns, not significant; p, points.

Negative connotations were mentioned in both diseases IPF or sarcoidosis and most prevalent were frustrating (39% IPF, 55% sarcoidosis), followed by exhausting (IPF 25%, sarcoidosis 37%) and annoying (IPF 33%, sarcoidosis 33%). In severely fatigued patients with IPF or sarcoidosis these percentages of negative connotations were even higher and also other negative connotations were substantially prevalent (>30%) as wearisome, incessant, upsetting, discouraging and inexplicable. Catastrophizing thoughts about fatigue are associated with higher rates of experiencing fatigue as frustrating,

exhausting, frightening and less rates of pleasant. So, for a better understanding of fatigue it is necessary to look at the severity of the fatigue on the one hand, and the perception of fatigue on the other hand. Moreover, patients without severe fatigue might experience negative associations concerning fatigue and patients with severe fatigue might not come up with very negative terms. In treatment of patients, it is useful to know how people view their fatigue, to connect with the perception of the patient and thus to find out what is desirable to change their cognitions and/or behavior. Treatment of fatigue can

Table 4 Correlations of the categories of the FQL with fatigue, dyspnea, catastrophizing, anxiety, depression and general health in patients with idiopathic pulmonary fibrosis or sarcoidosis

	FQL-Frustrating		FQL-Exhausting		FQL-Pleasant		FQL-Frightening	
	ρ	P	ρ	P	ρ	P	ρ	P
Idiopathic pulmonary fibrosis								
Fatigue (CIS-Fatigue)	0.322	<0.05	0.258	<0.05	-0.231	NS	0.351	<0.01
Dyspnea (mMRC)	0.350	<0.01	0.343	<0.01	0.235	NS	0.445	<0.01
Fatigue catastrophizing (FCS)	0.551	<0.01	0.504	<0.01	0.000	NS	0.642	<0.01
Anxiety (HADS-Anxiety)	0.228	NS	0.252	NS	-0.054	NS	0.466	<0.01
Depression (HADS-Depression)	0.172	NS	0.195	NS	0.141	NS	0.438	<0.01
General health (EQ-5D-5L VAS)	-0.355	<0.01	-0.369	<0.01	-0.021	NS	-0.350	<0.01
Sarcoidosis								
Fatigue (CIS-Fatigue)	0.597	<0.01	0.583	<0.01	-0.404	<0.01	0.320	<0.05
Dyspnea (mMRC)	0.393	<0.01	0.556	<0.01	-0.469	<0.01	0.296	<0.05
Fatigue catastrophizing (FCS)	0.608	<0.01	0.643	<0.01	-0.486	<0.01	0.650	<0.01
Anxiety (HADS-Anxiety)	0.250	NS	0.530	<0.01	-0.237	NS	0.484	<0.01
Depression (HADS-Depression)	0.531	<0.01	0.584	<0.01	-0.389	<0.01	0.421	<0.01
General health (EQ-5D-5L VAS)	-0.525	<0.01	-0.531	<0.01	0.537	<0.01	-0.169	NS

P, statistically significant; ρ , Spearman rank correlation coefficient. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L, EuroQol, 5 dimensions, 5 levels (standardised measure of health status); FCS, Fatigue Catastrophizing Scale; FQL, Fatigue Quality Scale; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale Anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale Depression; mMRC, modified Medical Research Council-Dyspnea; VAS, Visual Analogue Scale.

be recommended in many ways and one of the treatment options is cognitive behavioral therapy (CBT), a type of psychotherapy. CBT aims to influence cognitions and behaviors that are related to the experienced problems (28,29). CBT could be an intervention for reducing fatigue in patients with sarcoidosis or IPF, as is already seen in patients with sarcoidosis (30,31), cancer (32), chronic fatigue syndrome (33) and multiple sclerosis (34). CBT also aims at changing the patients' attitude towards fatigue and in that way changing the experience of fatigue. Patients with chronic conditions with more complex problematic conditions might be referred to pulmonary rehabilitation. In pulmonary rehabilitation, cognitive behavioral therapy is already integrated and considered for improving patients' physical, psychological and quality of life (35,36). In addition to this known information, this study emphasizes the importance of taking into account the patients' different perceptions of fatigue in the rehabilitation of the patients. Further research is needed to investigate the most targeted approach to reduce negative experiences of fatigue.

It has been established that fatigue and depression are highly correlated and depression symptomatology and prevalence are significantly increased in fatigued individuals (37). In patients with sarcoidosis the HADS-depression score is significantly related to negative expressions of fatigue, but, in patients with IPF only to frightening. In the current study severe fatigue was present in 48% of the patients with IPF and in 69% of the patients with sarcoidosis. The depression rate of moderate/severe level was present in 9% of the patients with IPF and in 8% of the patients with sarcoidosis. These data support that fatigue is a common symptom in many physical and psychological disorders, such as depression. But that doesn't mean that fatigue and depression are the same phenomenon. In other words, a fatigued patient does not necessarily have to be depressed.

The symptoms fatigue and sleepiness are often used intermingled, but the symptom excessive daytime sleepiness (ESS) describes the probability to fall asleep in various situations at daytime (38). This study and a recent study

Table 5 Correlations of general health (EQ-5D-5L-VAS and EQ-5D-5L-Index Value) in patients with idiopathic pulmonary fibrosis or sarcoidosis

	General health							
	Idiopathic pulmonary fibrosis				Sarcoidosis			
	EQ-5D-5L VAS		EQ-5D-5L IV		EQ-5D-5L VAS		EQ-5D-5L IV	
	ρ	P	ρ	P	ρ	P	ρ	P
Fatigue severity (CIS-Fatigue)	-0.529	<0.01	-0.414	<0.01	-0.710	<0.01	-0.577	<0.01
FQL-Frustrating category	-0.355	<0.01	-0.339	<0.01	-0.525	<0.01	-0.633	<0.01
FQL-Exhausting category	-0.369	<0.01	-0.377	<0.01	-0.531	<0.01	-0.703	<0.01
FQL-Pleasant category	-0.021	NS	0.013	NS	0.537	<0.01	0.604	<0.01
FQL-Frightening category	-0.350	<0.01	-0.485	<0.01	-0.169	NS	-0.415	<0.01
Dyspnea (mMRC)	-0.564	<0.01	-0.620	<0.01	-0.508	<0.01	-0.666	<0.01
Fatigue catastrophizing (FCS)	-0.537	<0.01	-0.672	<0.01	-0.327	<0.05	-0.574	<0.01
Anxiety (HADS-Anxiety)	-0.398	<0.01	-0.521	<0.01	-0.292	<0.05	-0.380	<0.01
Depression (HADS-Depression)	-0.414	<0.01	-0.625	<0.01	-0.489	<0.01	-0.656	<0.01
Age (years)	-0.157	NS	0.006	NS	0.026	NS	-0.070	NS
Gender	-0.100	NS	-0.012	NS	-0.171	NS	-0.297	<0.05
Comorbidity frequency	-0.361	<0.01	-0.245	NS	-0.223	NS	-0.340	<0.01
TLCO%Pred	0.417	<0.01	0.488	<0.01	0.168	NS	0.232	NS

P, statistically significant; ρ , Spearman rank correlation coefficient. CIS-Fatigue, Checklist Individual Strength subscale Fatigue; EQ-5D-5L IV, EuroQol, 5 dimensions, Index Value; EQ-5D-5L VAS, EuroQol, 5 dimensions, Visual Analog Scale; FCS, Fatigue Catastrophizing Scale; FQL, Fatigue Quality Scale; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale Anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale Depression; mMRC, modified Medical Research Council-Dyspnea; VAS, Visual Analogue Scale; TLCO %Pred, Transfer Factor of the lung for carbon monoxide (measured in mL/min/mmHg) percentage predicted.

Table 6 Regression equations for general health (EQ-5D-5L VAS or EQ-5D-5L index value) in patients with idiopathic pulmonary fibrosis or sarcoidosis

	Regression equation	R	R ²	SEE
IPF				
EQ-5D-5L VAS	80.700 – 0.529*CIS-Fatigue – 1.611*HADS-Anxiety – 5.440*Comorbidities + 0.339*TLCO%Pred	0.76	0.58	11.72
EQ-5D-5L index value	0.829 – 0.003*FQL-Exhausted – 0.032*mMRC – 0.011*HADS-Anxiety – 0.014*HADS-Depression + 0.003*TLCO%Pred	0.87	0.75	0.10
Sarcoidosis	Regression equation	R	R ²	SEE
EQ-5D-5L VAS	98.672 – 0.815*CIS-Fatigue + 0.340*FQL-Pleasant – 1.387*HADS-Depression	0.77	0.59	12.73
EQ-5D-5L index value	0.986 – 0.002*FQL-Exhausted – 0.070*mMRC – 0.019*HADS-Anxiety	0.75	0.56	0.15

Regression equations with backwards analysis, dependent variable EQ-5D-5L VAS or EQ-5D-5L index value, independent variables in univariate analyses significant (P<0.05) correlated; only equations are presented after the final backward regression analysis. CIS-Fatigue, Checklist Individual Strength subscale fatigue; EQ-5D-5L, EuroQol 5 dimensions 5 levels; FCS, Fatigue Catastrophizing Scale; FQL-Exhausted, Fatigue Quality List category exhausted; FQL-Pleasant, Fatigue Quality List category pleasant; HADS-Anxiety, Hospital Anxiety and Depression Scale subscale anxiety; HADS-Depression, Hospital Anxiety and Depression Scale subscale depression; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council dyspnea scale; TLCO %Pred, Transfer Factor of the lung for carbon monoxide percentage predicted; VAS, Visual Analog Scale.

of Bloem *et al.* [2020] showed a slight correlation between CIS-fatigue score and sleepiness (ESS>10) in patients with sarcoidosis ($\rho=0.282$; $P<0.05$) but not in patients with IPF. In the search for different experiences of fatigue is sleepiness not included. Remarkable in the study of Bosse Henck (38) severe fatigue in patients with sarcoidosis was found in (only) 16% of the total sample while in the current study it is much higher (i.e., 69%). Both studies used a different fatigue questionnaire, Bosse Henck used the Fatigue Assessment Scale (39-41) and current study used the CIS-Fatigue. The intracorrelation between the FAS and the CIS-Fatigue is to be expected seemly high. So differences in fatigue severity results is expected to be part of different sarcoidosis cohorts. The German cohort existed from members of the German Sarcoidosis Society in contrary of current study with a well-defined pulmonary sarcoidosis cohort.

A limitation of the current study is that all patients were recruited in an outpatient clinic of a respiratory medicine department. Therefore, these results may not be generalizable to patients with IPF or sarcoidosis in other settings. In addition, fatigued patients with negative perceptions of fatigue might not be willing to participate in a questionnaire-based fatigue study. Insights why patients were not responding have remained unknown due to inability to study non-participating patients. Strengths of the study are the cross-sectional design, the good distribution of patients between the non-severely and the severely fatigued groups and the relatively large sample size of the number of patients with IPF.

Conclusions

In conclusion, this is the first study investigating experiences of fatigue in patients with IPF or pulmonary sarcoidosis. Professionals treating patients with IPF or sarcoidosis not only should focus on fatigue severity, but also on the subjective experiences related to fatigue. In addition, not only severely fatigued patients may have negative fatigue-related experiences, but also non-severely fatigued patient may have these. Although similarities were found in the connotations of fatigue across non-severe and severe fatigued patients, differences were also evident and could be mapped for IPF and sarcoidosis.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Medical Ethical Committee approval was granted (METCZ20180027) and registration with the Netherlands Trial Register (Code 7201) was established, written informed consent was obtained.

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