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Fatigue in sarcoidosis and idiopathic pulmonary fibrosis: differences in character and severity between diseases

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Abstract. *Background:* Sarcoidosis and idiopathic pulmonary fibrosis (IPF) are two common forms of interstitial lung disease. Fatigue is a recognised feature of sarcoidosis but an association between IPF and fatigue has not been investigated. *Rationale:* To investigate the frequency and severity of fatigue in these groups, and variables affecting fatigue scores. *Methods:* A cross-sectional questionnaire study of patients with sarcoidosis and IPF followed-up at a single hospital was undertaken. Questionnaire data included validated measures of fatigue, anxiety, depression, sleepiness and dyspnoea, plus measures of disease severity including spirometry data. *Results:* Questionnaires were administered to 232 patients (82 healthy volunteers, 73 sarcoidosis patients and 77 IPF patients). Sarcoidosis patients had statistically higher sleepiness scores but no significant difference was seen between overall measures of fatigue, anxiety or depression. Stratification by severity revealed a non-statistically significant tendency towards more severe fatigue scores in sarcoidosis. Regression analysis failed to identify any significant predictor variables measured in the sarcoidosis cohort, though in the IPF group both dyspnoea and sleepiness scores were significant predictors of fatigue (R^2=0.74). *Conclusions:* Both sarcoidosis and IPF patients suffer with fatigue, although sarcoidosis patients tended towards reporting more severe fatigue scores, suggesting a subgroup with severe fatigue. The fatigue experienced by the two groups appears to be different; sarcoidosis patients report greater frequency of mental fatigue whereas IPF patients appear to suffer exhaustion, potentially related to dyspnoea. Dyspnoea and sleepiness scores modeled the majority of fatigue in the IPF group, whereas no single factor was able to predict fatigue in sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 130-138)*

Key words: sarcoidosis, idiopathic pulmonary fibrosis, fatigue, quality of life

Introduction

Fatigue in Sarcoidosis

Sarcoidosis, a systemic granulomatous disease of no known cause, affects people of all ethnic groups and ages. Worldwide incidence peaks between the ages of 20 and 39 (1), with UK incidence approximately 5 per 100,000 per year (2). Fatigue has been described as a "core symptom" of sarcoidosis (3), and is present in up to 80% of patients (4). A "post-sarcoidosis chronic-fatigue syndrome" has been described (8, 9) denoting the presence of fatigue in sarcoidosis patients with no evidence of active disease. It does not appear to be affected by age, duration of disease or treatment (7, 8). Fatigue is impossible to quantify using a physiological measure (9), but multiple questionnaires have been validated for its measurement. Fatigue can overlap with "sleepiness", denoting the desire for sleep, which can be assessed by the multiple sleep latency test (10). By contrast,

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fatigue is a subjective symptom with different aspects (physical and psychological) and is frequently described in many different terms by surveyed populations, making it a heterogenous entity that is much more difficult to pin down than the concept of sleepiness (11). In qualitative analysis patients highlighted the mental and physical aspects of fatigue leading to functional and social limitations and low energy (12). There is evidence to suggest that both sleepiness and fatigue are elevated in sarcoidosis patients. When screened using the Epworth Sleepiness Scale (ESS), sarcoidosis patients showed a higher frequency of hypersomnolence (indicated by an ESS score >9) than controls, even when adjusted for confounders (13).

There is significant overlap between depression and anxiety with fatigue in sarcoidosis. In one study, 35-36% of patients had symptoms of significant fatigue and anxiety, and 43-46% of patients had symptoms of both fatigue and depression, with 31% of the patients indicating high degrees of fatigue, depression and anxiety (14), and evidence to suggest that psychological distress and reduced health status are associated with fatigue, as well as reduced physical activity and muscle weakness (6). However, simultaneous measurement of multiple questionnaires investigating these factors has not yet been performed, and the interaction between them is therefore unclear.

Fatigue in IPF

Idiopathic pulmonary fibrosis (IPF) is a form of interstitial lung disease resulting in fibrosis of the parenchyma with an incidence is 6.8-16.3/100,000 (15) and median life expectancy of between 2.9 and 5 years (16) the spectrum of histopathological subgroups and their associated prognostic significance. The study group consisted of 54 men and 50 women with a median age of 63 yr. Median survival was 3.8 yr after diagnosis by open lung biopsy (OLB) with an estimated 10 yr survival of 27%. Current histopathologic review showed a heterogeneous group including usual interstitial pneumonia (UIP). Increasingly recognised is the prevalence of co-morbidities including depression, which can adversely impact quality of life, physical, psychosocial and economic problems (17).

In contrast to sarcoidosis the presence of fatigue in IPF patients has not been studied extensively. One study evaluated a wide range of issues affecting the quality of life of patients with IPF, including fatigue. Quality of life correlated most strongly with dyspnoea, suggesting that fatigue and energy levels worsen with increasing breathlessness (18). A further study noted that health-related quality of life differences between patients with IPF are partly explained by differences in fatigue as well as dyspnoea (19). No studies have investigated the effect of depression on fatigue in IPF, but depression is a common problem in IPF cohorts, independent of disease severity, age, duration since diagnosis or co-morbidities (20).

In this study we aimed to investigate the differences in fatigue experienced by IPF and sarcoidosis patients and its relationship with depression, sleepiness and dyspnoea, through the administration of questionnaires, and markers of pulmonary function, as well as any possible differences in how fatigue is experienced by each group. No previous trial has directly compared the degree of fatigue experienced by these two groups of patients.

Methods

Patients under the care of the respiratory department at the Norfolk and Norwich University Hospital with a diagnosis of IPF and sarcoidosis were identified from an electronic database of ILD patients, by their primary consultant physician within clinic, or from patient support days run by the respiratory research group for patients with sarcoidosis or IPF. Consent was gained for the use of their pulmonary function (including Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC) and FEV1/FVC ratio) and radiological data to determine disease severity.

A control population of healthy volunteers was recruited from the community, via adverts placed in local media and through relatives of patients seen in outpatients. The clinical notes of healthy volunteers were not reviewed.

Study Population

Participants were eligible for inclusion if they were over the age of 18, had a diagnosis of IPF or sarcoidosis, were able to give informed consent to take part in the study, and did not have any major co-morbidities aside from their diagnosed lung disease.

Healthy volunteers were eligible for inclusion if they had no significant medical co-morbidity.

IPF patients were included if they met the diagnostic criteria for IPF described by the America Thoracic Society's 2011 guidelines (21). Patients in the sarcoidosis group required histological evidence of granuloma formation consistent with sarcoidosis plus radiological evidence of pulmonary involvement (22). Patients with normal chest X-rays but abnormal CT scans were included.

Study Measurements

The questionnaires administered are detailed below. Appropriate permissions were received before any questionnaires were administered or data collected. Questionnaires were presented to participants in a pack containing the questionnaires in the order presented below, with the questionnaires completed in the presence of investigators. Questionnaire results were entered onto a database and a selection double-checked for data accuracy. Data collection occurred over an eighteen-month period, between September 2012 and March 2014. Questionnaires chosen for inclusion were:

(1) Hospital Anxiety and Depression Scale (HADS) (23)
(2) EuroQoL 5D (EQ5D) (24)
(3) Kings Brief Interstitial Lung Disease questionnaire (K-BILD) (25)
(4) MRC dyspnoea scale (26)
(5) Epworth Sleepiness Scale (ESS) (27)studies of sleep in patients with interstitial lung disease revealed disturbed sleep, frequent nocturnal desaturations, nocturnal cough, and obstructive sleep apnea (OSA
(6) Fatigue Assessment Scale (FAS) (28)
(7) St George's Respiratory Questionnaire (SGRQ) (29,30)the St. George's Respiratory Questionnaire (SGRQ
(8) Patient demographics (non-validated questionnaire)

Statistical Analysis

Continuous data were assessed for skewness to determine if the results are normally distributed, with analysis performed using analysis of variance (ANOVA).

Analysis of categorical data was performed using the chi-squared test where appropriate. This analysis was also performed on the stratified data from the HADS, ESS and FAS scales to compare the number of patients within each group reporting results compatible with anxiety, depression, severe sleepiness (and the possibility of sleep-disordered breathing syndromes) and pathological levels of fatigue.

Further analysis was undertaken within the IPF and sarcoidosis groups to explore relationships between fatigue and various predictor variables (questionnaire score results and disease severity measures as described above). This was performed using linear regression analyses to investigate evidence of a relationship between FAS scores and the predictor variables.

Analysis of correlation between FAS scores and potential predictors of fatigue (age, dyspnoea score, depression and anxiety scores, sleepiness and spirometric indices) was performed and displayed visually in scatterplot form. Assuming a linear association, the relationships between these factors and fatigue (measured by FAS score) were tested using linear regression.

After analysing raw data, patients were stratified using pre-existing scoring systems within questionnaires. This allows a review of the prevalence of patients with questionnaire scores suggesting abnormal fatigue, sleepiness, depression and anxiety. The scores for each stratum are shown in the results table.

Data was collated on a Microsoft Excel spreadsheet and analysed using IBM SPSS version 19 (SPSS version 19, IBM Company).

Study Conduct and Considerations

The study received ethics committee approval, reference 12/EM/0413.

Results

Questionnaires were administered to a total of 232 patients, comprising 82 healthy volunteers, 73 sarcoidosis patients and 77 IPF patients. The demographics are shown in table 1. IPF patients were significantly older, although no association between age and fatigue scores was found. A higher proportion of men was seen in the IPF cohort (76.4%), whilst the

Table 1. Demographics

		Healthy Volunteers	Sarcoidosis	IPF
Total Number		82	73	77
Mean Age (S.D.)		53.6 (16.7)	59.4 (13.4)	76.4 (7.5)
Sex – Male (%)		36 (43.9)	40 (54.8)	59 (76.6)
Current smokers (%)		26 (34.2)	0 (0)	3 (3.9)
Ex-smokers (%)		14 (17.1)	30 (41.1)	61 (79.2)
Mean Pack/years history (S.D.)		15.3 (13.4) 12.5 (11.5)	27.2 (24.6)	
MRC Dyspnoea grade*	1 (%)	63 (78.8)	14 (20.3)	8 (10.6)
	2 (%)	13 (16.3)	29 (42.0)	29 (38.7)
	3 (%)	4 (5.0)	15 (21.7)	23 (30.7)
	4 (%)	0 (0)	10 (14.5)	9 (12.0)
	5 (%)	0 (0)	1 (1.4)	6 (8.0)
Spirometry (percentage predicted)	FEV1	-	88.6 (21.8)	-
	FVC	-	98.0 (20.4)	84.3 (19.8)
	TLCO	-	76.5 (16.5)	51.1 (18.8)

*2 MRC dyspnoea score datasets missing from IPF and health volunteer cohorts, 4 missing from the sarcoidosis cohort

sarcoidosis and healthy volunteer cohorts were closer to a 1:1 ratio. A higher proportion of patients with IPF had formerly smoked, and with a much higher pack-year history. By contrast, a much higher proportion of patients in the healthy volunteer group were currently smoking. Although both IPF and sarcoidosis patients had the greatest proportions in the grade 0 and grade 1 breathlessness, a larger number of patients in the IPF group classified themselves as suffering the highest level of dyspnoea, with 8% of respondents with IPF indicating that they were suffering grade 5 dyspnoea.

The majority of IPF patients included had mild or limited disease, with only 22.1% patients being classified as severe disease (TLCO <40% predicted (31)). In the sarcoidosis cohort over half (58.1%) of the patients surveyed had normal spirometry with airflow obstruction in 24.2%, restrictive defect in 8.1% and a mixed deficit in 9.7% of patients. Within the sarcoidosis cohort 32.9% of the cohort receiving prednisolone or the steroid sparing agents methotrexate and azathioprine, and 31.6% of patients had evidence of extra-pulmonary involvement.

Questionnaire results, displayed as mean values in each of the groups, are shown in table 2, The data from the KBILD questionnaire showed that scores were much higher in the healthy volunteers group when compared with the sarcoidosis and IPF cohorts, with IPF cohorts having the lowest scores. This difference did not reach statistical significance (p=0.084). IPF patients also had the lowest EQ5D health rating scores, but these were again non-significant statistically when compared with the sarcoid cohort (p=0.513). The HADS-A and HADS-D questionnaires indicated that higher levels of anxiety and depression were found in the IPF and sarcoidosis cohorts compared with healthy volunteers. The differences between the sarcoidosis and IPF groups did not reach statistical significance, though there was a trend towards greater levels of anxiety in the sarcoidosis group compared with the IPF patients (mean scores 6.6 vs 5.4, p=0.080). No differences between IPF and sarcoidosis patients were seen in the mean FAS values, or the symptoms and impacts domains of the SGRQ. The results do show a statistically significant increase in ESS score in sarcoidosis patients compared with IPF patients (8.0 vs 5.7, p=0.003). By contrast, IPF patients were seen to have worse scores in the SGRQ activities domain and total SGRQ score compared with the sarcoidosis group (SGRQ activities mean value 59.3 vs 49.0, p=0.031 and total SGRQ score 42.7 vs 34.8, p=0.034).

Table 3 shows the results when stratified into pre-existing levels indicating scores consistent with clinical abnormalities. The HADS-A scale showed that although there is a trend towards more patients

Table 2. Questionnaire results

Questionnaire Mean (S.D.)	Healthy Volunteers	Sarcoidosis	IPF	p-value* (IPF vs Sarcoid)†
KBILD	99.2 (17.2)	78.7 (17.5)	73.1 (19.9)	0.084
HADS-A	4.0 (3.2)	6.6 (3.9)	5.4 (4.0)	0.080
HADS-D	2.1 (2.4)	5.1 (4.0)	4.7 (3.8)	0.530
EQ5D No.	81.1 (21.4)	65.3 (21.2)	62.9 (22.0)	0.513
ESS	4.7 (4.4)	8.0 (4.4)	5.7 (4.3)	**0.003**
FAS	16.8 (6.1)	24.7 (9.2)	23.1 (7.3)	0.272
SGRQ – Symptoms	9.4 (15.6)	39.9 (26.7)	43.7 (23.3)	0.382
SGRQ – Activities	12.4 (16.8)	49.0 (27.7)	59.3 (26.8)	**0.031**
SGRQ – Impacts	3.5 (9.4)	26.4 (21.3)	32.4 (19.1)	0.095
SGRQ – Total	7.4 (11.5)	34.8 (21.4)	42.7 (20.2)	**0.034**

*t-test performed to compare means as minimal skewness of data; values <+/-1 within sarcoidosis and IPF cohorts suggested normally distributed data.
†All questionnaire scores were significantly different (p<0.001) between IPF/Sarcoidosis and healthy volunteers.

Table 3. Prevalence of anxiety, depression, sleepiness and fatigue symptoms†

		Healthy Volunteers (A)	Sarcoidosis (B)	IPF (C)	p-value*
HADS-A – Anxiety	Normal (%) *- Score 0-7*	73 (89.0)[BC]	42 (60.9)	54 (71.4)	**0.008**
	Mild (%) *- Score 8-10*	5 (6.1)	18 (26.1)[A]	14 (18.2)	
	Moderate (%) *- Score 11-14*	3 (36.6)	8 (11.6)	6 (7.8)	
	Severe (%) *- Score 15-21*	1 (1.2)	1 (1.4)	2 (2.6)	
HADS-D - Depression	Normal (%) *- Score 0-7*	78 (95.1)[BC]	51 (73.9)	63 (82.9)	**0.004**
	Mild (%) *- Score 8-10*	3 (36.6)	10 (14.5)	3 (3.9)	
	Moderate (%) *- Score 11-14*	1 (1.2)	5 (7.2)	8 (10.6)[A]	
	Severe (%) *- Score 15-21*	0 (0)	3 (4.3)[A]	2 (2.6)[A]	
Epworth Sleepiness Scale	No sleepiness (%) *- Score 0-9*	66 (85.7)[B]	47 (67.1)	52 (85.2)[B]	**0.027**
	Borderline (%) *- Score 10-15*	7 (9.1)	19 (27.1)[A]	7 (11.5	
	Severe (%) *- Score 16-24*	4 (5.2)	4 (5.7)	2 (3.3)	
Fatigue Assessment Scale	Normal (%) *- Score 0-21*	74 (91.4)[BC]	34 (49.3)	40 (54.8)	**<0.001**
	Fatigued (%) *- Score 22-34*	5 (6.2)	27 (39.1)[A]	30 (41.1)[A]	
	Severe (%) *- Score 35-50*	2 (2.4)	8 (11.6)	3 (4.1)	

*Results are based on two-sided tests with significance level 0.05. For each significant pair, the key of the category with the smaller proportion appears under the category with the larger column proportion. For example, there is a larger proportion of patients with a normal HADS-A score in the healthy volunteer column ([A]) than the sarcoidosis ([B]) and IPF ([C]) columns, so the letters [BC] appears in the healthy volunteer column.
†Due to incomplete responses for some questionnaires there are fewer patients stratified by depression, anxiety, sleepiness and fatigue than there were enrolled in the study.

with IPF having mild or moderate anxiety, only the sarcoidosis cohort had a statistically greater number of patients scored as having mild anxiety compared with the other groups. For the HADS-D scores, there were a greater number of patients in the sarcoidosis and IPF cohorts who scored highly enough to indicate severe depression, with more patients in the IPF group scoring moderate levels of depression. The results from the ESS showed that a larger number of patients with sarcoidosis had borderline levels of sleepiness compared with healthy volunteers and IPF patients, although there was no difference between the groups in the number of patients classified as severely sleepy. The FAS scores showed that the IPF and sarcoidosis cohorts had a greater number of patients with significant fatigue (scoring 22-34 points) compared with healthy volunteers. There was no statistical difference in patients reporting FAS scores of 35 points or more between all three groups, although there was trend towards more patients reporting severe fatigue in the sarcoidosis cohort (11.6% of sarcoidosis patients, compared with 4.1% of IPF patients and 2.4% of healthy volunteers).

Correlation between FAS scores and participant age, MRC, HADS-A, HADS-D, ESS, and spirometry results (FVC and TLCO, plus FEV1 in the sarcoidosis cohort) was performed with visual plotting of data showing linear relationships. When FAS score was predicted using linear regression models in sarcoidosis patients, none of the predictor variables included in the model were significant (table 4(a)), with the overall model fit R^2=0.50. By contrast, when FAS was predicted in IPF patients it was found that MRC dyspnoea scores (β=0.47, p<0.001) and ESS results (β=0.32, p=0.003) were significant predictors (table 4(b)). The overall model fit for the IPF cohort was R^2=0.74.

Scores within the FAS results were also compared. Three domains of the FAS questionnaire showed significant differences between IPF and sarcoidosis cohorts. Those with sarcoid reported higher scores in domain 2 ("I get tired very quickly"; 3.10 vs 2.60, p=0.013), domain 7 ("I have problems thinking clearly"; 2.10 vs 1.75, p=0.050) and domain 9 ("Mentally, I feel exhausted"; 2.32 vs 1.81, p=0.003). All other domains showed no statistical difference between the IPF and sarcoidosis cohorts.

Discussion

This is the first paper to simultaneously examine the issues affecting fatigue in sarcoidosis and IPF, and to compare the differences between these groups. The inclusion of spirometry, depression scores, sleepiness scores and fatigue in the same cohort allows modeling of the relationships between these, and assessment of how much of fatigue can be explained by these variables, all of which have been suggested

Table 4. Regression co-efficients of FAS scores on predictor variables (Sarcoidosis and IPF patients)

Predictor Variable	Regression Co-efficient	95% C.I.	Standardised co-efficient	P value
(a) Sarcoidosis Cohort				
Age	-0.06	-0.23, 0.12	-0.09	0.516
MRC Dyspnoea	2.44	-0.57, 5.44	0.26	0.108
HADS-A	0.37	-0.44, 1.17	0.17	0.361
HADS-D	0.70	-0.13, 1.52	0.33	0.094
ESS	0.37	0.1, 0.93	0.19	0.186
FVC	0.04	0.26, 0.33	0.08	0.808
TLCO	-0.08	0.26, 0.11	-0.14	0.412
FEV_1	0.03	0.23, 0.29	0.07	0.817
(b) IPF Cohort				
Age	0.02	-0.08. 0.11	0.03	0.733
MRC Dyspnoea	2.97	1.40, 4.54	0.47	**<0.001**
HADS-A	0.17	-0.27, 0.60	0.09	0.443
HADS-D	0.35	-0.79, 0.90	0.18	0.192
ESS	0.53	0.19, 0.90	0.32	**0.003**
FVC	-0.01	-0.07, 0.06	-0.02	0.830
TLCO	0.00	-0.08, 0.09	0.01	0.961

as contributing to fatigue scores in either or both of these conditions.

Previous research has suggested that fatigue is one of the most important symptoms in predicting quality of life in sarcoidosis (32), but the results from our population show that it is also important in IPF patients. Our findings suggest that fatigue should be actively explored in patients with symptomatic IPF, as well sarcoidosis. Compared with sarcoidosis patients, IPF patients had equally poor FAS scores and worse quality of life scores. No relationship was seen between age, sleepiness, anxiety or depression, dyspnoea or spirometry measures in the sarcoidosis cohort, in contrast to the IPF group, where increasing dyspnoea (measured by the MRC dyspnoea scale) had an effect on increasing fatigue. This may reflect the systemic nature of sarcoidosis whereas IPF primarily damages the lungs.

It was notable that there was a lack of association between common markers of disease severity and fatigue in sarcoidosis patients. Sarcoidosis predominantly affects the chest, with 85 to 95% of patients having an abnormal chest X-ray at diagnosis (33), and up to 50% suffering respiratory symptoms including dyspnoea, cough, chest tightness or pain (34). As these patients were obtained from a respiratory clinic, the markers of severity chosen were predominantly respiratory in nature; chest X-ray severity, pattern of pulmonary function testing abnormality, as well as current use of immunosuppression and presence of extra-pulmonary disease. However, none of these measures showed a relationship with change in FAS score. This may reflect sub-clinical disease activity, such as small-fibre neuropathy and neurosarcoidosis. Both of these manifestations of sarcoidosis may not be readily apparent clinically, and both of which have been associated with fatigue in sarcoidosis (35,36). However, previous studies have failed to show that active inflammation is associated with fatigue at all (37, 38). The results from this study confirm this lack of clear association with aspects of sarcoidosis disease activity, although no data regarding biomarkers suggesting disease activity was undertaken here.

The interplay between fatigue and measures of sleepiness and depression in sarcoidosis is complex as has been alluded to previously (38). The higher ESS scores in the sarcoidosis cohort suggests that patients with sarcoidosis are not only fatigued but also sleepy, with more fatigued patients reporting greater symptoms of sleepiness, and the previously documented increase in sleep-disordered breathing syndromes in sarcoidosis patients could explain this (39). However, even when appropriately treated not all sarcoidosis patients who were found to have obstructive sleep apnoea (OSA) on polysomnography had resolution of symptoms (40), suggesting that the fatigue seen is due to more than just sleep-disordered breathing syndromes including OSA. Also, the presence of sleepiness did not predict fatigue scores in the regression analysis, suggesting that the fatigue suffered by sarcoidosis patients is not directly related to sleepiness. Depression was seen to correlate moderately strongly with fatigue scores, which is again in keeping with previous work suggesting that there is overlap between fatigue and depression (14) but depression also did not predict fatigue in the regression model. When all factors were combined, the lack of ability to model fatigue scores from the recorded variables reinforces the complex nature of fatigue found in sarcoidosis.

The review of individual domain scores within the FAS revealed differences between IPF and sarcoidosis cohorts. Sarcoidosis patients reported greater problems with mental fatigue than IPF patients, linking with the higher ESS scores reported in the sarcoidosis cohort. Fatigue experienced by IPF and sarcoidosis patients appears quite different. IPF patients appear fatigued due to lack of energy, rapidly becoming exhausted and tired performing any tasks, whilst sarcoidosis patients are mentally exhausted. However, the FAS score is not validated for this analysis of sub-sections. Although the difference in scores between IPF and sarcoidosis patients may be statistically significant it is not possible to confirm that this is a clinically significant difference in the subsections of fatigue. Further evaluation of this may be best explored using interviews or focus groups with qualitative analysis, which may help to confirm a difference in how patients describe their experience of fatigue.

This study examined a cross-sectional cohort of IPF and sarcoidosis patients at a single point, and as such does not include any longitudinal data to review change in scores over time. Further evidence is required looking at the difference between fatigue in IPF and sarcoidosis patients, which may require analysis of qualitative aspects (patient de-

scriptions), measures of exercise (both physical capability, as measured by a 6 minute walk test, and physical activity levels, measured using accelerometers) and measures of disease activity in sarcoidosis, which were aspects not covered in this trial. The lack of disease-specific quality of life questionnaires (such as the King's Sarcoidosis Questionnaire (41), which had not been validated at the start of this trial) is also limiting, and could be improved in further work. Finally, we did not include measurements of biomarkers of disease activity for either disease cohort. Addressing these points will help to further clarify the relationship between fatigue and disease in both IPF and sarcoidosis.

Our study emphasises the lack of association between fatigue and disease activity in sarcoidosis, while providing further evidence that it cannot be explained or modeled by levels of depression, anxiety or sleepiness experienced by patients. It also appears very different in character to the fatigue experienced by IPF patients, which occurs more due to dyspnoea from disease progression. However, fatigue is an important symptom in both IPF and sarcoidosis and should be explored with patients being seen in clinic. This is particularly important in sarcoidosis where markers of disease activity commonly measured as part of their routine care cannot predict the severity of fatigue.

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References

1. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 1997 Feb 1; 145(3): 234-41.
2. Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006 Nov; 61(11): 980-5.
3. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006 Oct; 130(4): 989-94.
4. De Kleijn WPE, De Vries J, Lower EE, Elfferich MDP, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. Curr Opin Pulm Med 2009 Sep; 15(5): 499-506.
5. James DG. Complications of sarcoidosis. Chronic fatigue syndrome. Sarcoidosis 1993 Mar; 10(1): 1-3.
6. Korenromp IHE, Heijnen CJ, Vogels OJM, van den Bosch JMM, Grutters JC. Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. Chest 2011 Aug; 140(2): 441-7.
7. Hinz A, Fleischer M, Brähler E, Wirtz H, Bosse-Henck A. Fatigue in patients with sarcoidosis, compared with the general population. Gen Hosp Psychiatry 2011 Oct; 33(5): 462-8.
8. Marcellis RGJ, Lenssen AF, Elfferich MDP, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 2011 Sep; 38(3): 628-34.
9. Vucinić V, Stojković M, Milenković B, et al. Fatigue in sarcoidosis: detection and treatment. Srp Arh Celok Lek 2012 Feb; 140(1-2): 104-9.
10. Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol 1978 Nov; 45(5): 621-7.
11. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev 2006 Feb; 10(1): 63-76.
12. Victorson DE, Cella D, Grund H, Judson MA. A conceptual model of health-related quality of life in sarcoidosis. Qual Life Res Int J Qual Life Asp Treat Care Rehabil 2013 May 26;
13. Patterson KC, Huang F, Oldham JM, Bhardwaj N, Hogarth DK, Mokhlesi B. Excessive daytime sleepiness and obstructive sleep apnea in patients with sarcoidosis. Chest 2013 Jun; 143(6): 1562-8.
14. De Kleijn WPE, Drent M, De Vries J. Nature of fatigue moderates depressive symptoms and anxiety in sarcoidosis. Br J Health Psychol 2013 May; 18(2): 439-52.
15. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2006 Oct 1; 174(7): 810-6.
16. Bjoraker JA, Ryu JH, Edwin MK et al. Prognostic Significance of Histopathologic Subsets in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 1998 Jan 1; 157(1): 199-203.
17. Lee AS, Mira-Avendano I, Ryu JH, Daniels CE. The burden of idiopathic pulmonary fibrosis: An unmet public health need. Respir Med 2014 Jul; 108(7): 955-67.
18. Swigris JJ, Kuschner WG, Jacobs SS, Wilson SR, Gould MK. Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review. Thorax 2005 Jul; 60(7): 588-94.
19. Lubin M, Chen H, Elicker B, Jones KD, Collard HR, Lee JS. A comparison of health-related quality of life in idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. Chest 2014 Jun 1; 145(6): 1333-8.
20. Akhtar AA, Ali MA, Smith RP. Depression in patients with idiopathic pulmonary fibrosis. Chron Respir Dis. 2013 Aug; 10(3): 127-33.
21. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011 Mar 15; 183(6): 788-824.
22. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. Eur Respir J 1999 Oct; 14(4): 735-7.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun; 67(6): 361-70.
24. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997 Nov; 35(11): 1095-108.
25. Patel AS, Siegert RJ, Brignall K et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax 2012 Sep; 67(9): 804-10.
26. Stenton C. The MRC breathlessness scale. Occup Med Oxf Engl 2008 May; 58(3): 226-7.
27. Lancaster LH, Mason WR et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. Chest 2009 Sep; 136(3): 772-8.
28. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fa-

tigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004 Sep; 9(Pt 3): 279-91.
29. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992 Jun; 145(6): 1321-7.
30. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. Chest 1999 Nov; 116(5): 1175-82.
31. Egan JJ, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis: the potential for a simple classification. Thorax 2005 Apr; 60(4): 270-3.
32. Michielsen HJ, Peros-Golubicic T, Drent M, De Vries J. Relationship between symptoms and quality of life in a sarcoidosis population. Respir Int Rev Thorac Dis 2007; 74(4): 401-5.
33. Lynch JP, Ma YL, Koss MN, White ES. Pulmonary sarcoidosis. Semin Respir Crit Care Med 2007 Feb; 28(1): 53-74.
34. Mihailovic-Vucinic V, Jovanovic D. Pulmonary sarcoidosis. Clin Chest Med. 2008 Sep; 29(3): 459-473, viii-ix.
35. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med 1997 Apr; 102(4): 357-64.
36. De Kleijn WPE, Drent M, Vermunt JK, Shigemitsu H, De Vries J. Types of fatigue in sarcoidosis patients. J Psychosom Res 2011 Dec; 71(6): 416-22.
37. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord 2004 Jun; 21(2): 127-36.
38. Eklund A, du Bois RM. Approaches to the treatment of some of the troublesome manifestations of sarcoidosis. J Intern Med 2014 Apr; 275(4): 335-49.
39. Turner GA, Lower EE, Corser BC, Gunther KL, Baughman RP. Sleep apnea in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord 1997 Mar; 14(1): 61-4.
40. Mostard RLM, Vöö S, van Kroonenburgh MJPG et al. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. Respir Med 2011 Dec; 105(12): 1917-24.
41. Patel AS, Siegert RJ, Creamer D et al. The development and validation of the King's Sarcoidosis Questionnaire for the assessment of health status. Thorax 2013 Jan; 68(1): 57-65.