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Everyday cognitive failure and depressive symptoms predict fatigue in sarcoidosis: A prospective follow-up study

Celine Hendriks[a,b,c], Marjolein Drent[a,c,d,*], Willemien De Kleijn[a,e], Marjon Elfferich[a], Petal Wijnen[a,f], Jolanda De Vries[a,g,h]

[a] ILD Care Foundation Research Team, Ede, The Netherlands
[b] Faculty of Medicine, Utrecht University, Utrecht, The Netherlands
[c] ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, The Netherlands
[d] Dept. of Pharmacology and Toxicology, Faculty of Health, Medicine and Life Science, Maastricht University, Maastricht, The Netherlands
[e] Dept. of Psychology and Artificial Intelligence, Radboud University, Nijmegen, The Netherlands
[f] Central Diagnostic Laboratory, Maastricht University Medical Centre, Maastricht, The Netherlands
[g] Dept. of Medical Psychology, St. Elisabeth Hospital Tilburg, Tilburg, The Netherlands
[h] Dept. of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands

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ABSTRACT

Background: Fatigue is a major and disabling problem in sarcoidosis. Knowledge concerning correlates of the development of fatigue and possible interrelationships is lacking.
Objective: A conceptual model of fatigue was developed and tested.
Methods: Sarcoidosis outpatients (n = 292) of Maastricht University Medical Center completed questionnaires regarding trait anxiety, depressive symptoms, cognitive failure, dyspnea, social support, and small fiber neuropathy (SFN) at baseline. Fatigue was assessed at 6 and 12 months. Sex, age, and time since diagnosis were taken from medical records. Pathways were estimated by means of path analyses in AMOS.
Results: Everyday cognitive failure, depressive symptoms, symptoms suggestive of SFN, and dyspnea were positive predictors of fatigue. Fit indices of the model were good.
Conclusions: The model validly explains variation in fatigue. Everyday cognitive failure and depressive symptoms were the most important predictors of fatigue. In addition to physical functioning, cognitive and psychological aspects should be included in the management of sarcoidosis patients.

1. Introduction

The clinical manifestation, natural history, and prognosis of sarcoidosis are highly variable, and its course is often unpredictable [1]. Clinical manifestations vary with the organs involved [1,2]. While the lungs are affected in approximately 90% of patients with sarcoidosis, the disease frequently also involves lymph nodes, skin, and eyes. Interpretation of the severity of sarcoidosis can be complicated by its heterogeneity. Apart from lung-related symptoms, patients may suffer from a wide range of rather nonspecific symptoms [2–4]. Sarcoidosis-related complaints, including fatigue, general and muscle weakness, exercise limitation, pain, depressive symptoms, and cognitive failure may become chronic and persist even after all other signs of disease activity have disappeared [5–7].

Fatigue is the most frequently described and devastating symptom in sarcoidosis and is globally recognized as a disabling problem [3]. The reported prevalence varies from 60% to 90% of sarcoidosis patients, and up to 25% of fatigued sarcoidosis patients report extreme fatigue [3]. It affects patients' quality of life (QoL), i.e. their social life, and physical as well as psychological capacities [8–14]. Strookappe et al. showed that exercise capacity partly predicts patients' fatigue scores [15]. In their study, fatigue was not explained by lung function test results, inflammatory markers, or other clinical parameters.

The etiology of sarcoidosis is poorly understood and is likely to be multifactorial, encompassing active inflammation, cytokine release, depression, sleep disturbance, and/or small fiber neuropathy (SFN) [3,4,16]. Furthermore, fatigue can be caused by systemic treatments used to treat sarcoidosis, such as corticosteroids [6,17].

The diagnosis of sarcoidosis-associated fatigue requires extensive evaluation to identify and treat potentially reversible causes [3,12]. Its etiology may involve granuloma formation and cytokine release. However, despite effective treatment of the sarcoidosis activity, many

* Corresponding author. ILD Center of Excellence, St. Antonius Hospital Koekoekslaan 1, 3435 CM, Nieuwegein, The Netherlands.
E-mail address: m.drent@antoniusziekenhuis.nl (M. Drent).

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patients continue to experience fatigue, causing limitations [3,16,18].

Symptoms of fatigue and dyspnea induce exercise limitation, and fatigue also leads to physical inactivity. Although less recognized than exertional dyspnea, it is a very common and frustrating physical symptom in patients with sarcoidosis. Decreased physical activity can induce general deconditioning, which in turn contributes to increased perceived physical fatigue and a sense of dyspnea, lack of energy, or exhaustion [19,20]. Additionally, other symptoms reported by patients with sarcoidosis, including everyday cognitive deficits [12], depressive symptoms [21], anxiety, and symptoms associated with SFN [22], are also related to fatigue. Comorbidities associated with sarcoidosis, including depression, anxiety, hypothyroidism, and altered sleep patterns, all contribute to fatigue [6,23,24].

It is important to examine the potential factors that sustain fatigue in sarcoidosis. This may be accomplished by understanding clinical, psychological, and social predictors of fatigue in these patients. The knowledge concerning correlates of the development of fatigue and possible interrelationships is still incomplete, and previous research has mainly had a cross-sectional design [22] and studied the variables individually, instead of simultaneously. Therefore, the aim of the present study was to test a conceptual model of fatigue that includes physical and psychological symptoms.

2. Material and methods

2.1. Development model of fatigue

A conceptual model of fatigue, based on the model of Taylor and Aspinwall [25], was developed and tested. This conceptual model is represented in Fig. 1. Clinical variables were not incorporated in this model, because previous studies showed no consistent significant relationships between the fatigue assessment scale (FAS) and medical data widely used in sarcoidosis [22]. Time since diagnosis, sex, and age were incorporated into this model to control for background variation. Trait anxiety was expected to predict stressors, social support, and fatigue.

2.2. Study design and subjects

All sarcoidosis outpatients (n = 588) of the ILD Care Center of the Department of Respiratory Medicine of the Maastricht University Medical Center, a tertiary referral center in the Netherlands, were asked to participate. Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchoalveolar lavage fluid analysis results, according to the guidelines of the World Association of Sarcoidosis and Other Granulomatous Disorders [1]. The exclusion criteria were poor command of the Dutch language (n = 3) and relevant co-morbidity, such as malignancy (n = 7), dementia (n = 1), and a history of psychiatric illness (n = 2). Thirteen patients were found to be non-eligible and 133 patients refused to participate. The remaining 348 patients participated at baseline. After 12 months, 292 patients remained in the study.

2.3. Procedure

The patients received information about the study by e-mail and were asked to return an informed consent form if they were willing to participate. Patients who agreed to participate received the first set of questionnaires and were asked to return the completed set to the hospital in an enclosed envelope. After 6 and 12 months, patients received another set of questionnaires with an envelope. The most common reason for not completing the set of questionnaires was 'insufficient time'. The data were collected by the ILD care team. The Medical Ethics Committee of MUMC+ (MEC 07-4-015) approved the study protocol, and written informed consent was obtained from all patients.

2.4. Measurements

2.4.1. External resources and background variables

The following variables were taken as exogenous: gender (0 = male, 1 = female), age, and time since diagnosis.

2.4.2. Personal resource

At baseline the patients completed the State and Trait Anxiety Inventory (STAI) [26] to measure trait anxiety. Trait anxiety concerns differences between individuals in their disposition to respond to stressful situations with varying amounts of stress. The trait scale consists of 20 statements and asks people to describe how they generally feel. The psychometric characteristics of the Dutch version of this questionnaire are well established and considered good. High trait anxiety was defined as a score above 40, based on Dutch norm scores [26].

2.4.3. Questionnaires (stressors)

At baseline, the patients completed the Center for Epidemiological Studies-Depression Scale (CES-D) [27], the Small Fiber Neuropathy Screenings List (SFNSL) [28], and the Cognitive Failure Questionnaire (CFQ) [29]. In addition, patients were asked to determine their Borg Dyspnea Index (BDI) [30]. The CES-D [27] is a 20-item scale designed to measure the presence and degree of depressive symptoms. Scores of 16 or above are indicative of a depressive disorder. Reliability and

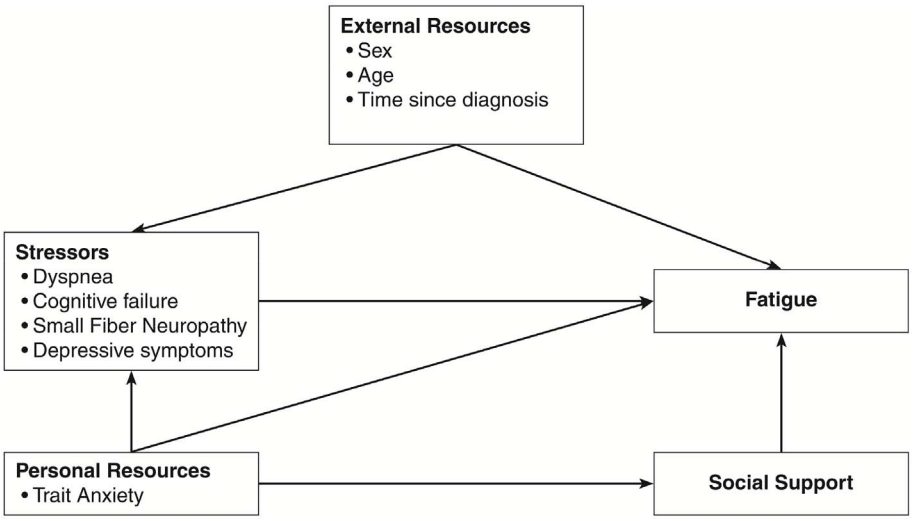

Fig. 1. Initial conceptual model of fatigue in sarcoidosis.[a]
[a] Error terms are omitted from this figure. All predictors were measured at baseline, and fatigue at 12 months follow-up.

criterion validity appear to be good [31]. The SFNSL is a short and easy to administer questionnaire to screen for symptoms related to SFN. It is a 21-item self-administered measure of symptomatology related to SFN. The response scale is a five-point scale (0 never to 4 always); scores on the SFNSL can range from 0 to 84. The cut-off score of the SFNSL is 11: a score below 11 indicates no or a few symptoms related to SFN, a score of 11–48 indicates probable or highly likely SFN, while a score above 48 is indicative of SFN [28]. The CFQ is a self-report questionnaire consisting of 25 items assessing impairment regarding attention, perception, memory, and motor functioning in everyday life [29]. The total CFQ score was calculated by adding up all items, with a total score ranging from 0 to 100. A higher score indicates more subjective cognitive impairment. The BDI is a self-rated scale for dyspnea. Scores ranges from 0 (no impairment) to 10 (severe impairment) [30].

2.4.4. Social support

At baseline, the patients also completed the Perceived Social Support Scale (PSSS) [32]. The total score of the 12-item version of the PSSS was used to assess general perception of social support. The rating scales ranged from 1, very strongly disagree, to 7, very strongly agree. The PSSS has good reliability and validity in patients undergoing coronary angiography [33], and has been translated into Dutch [32].

2.5. Health outcome

The Fatigue Assessment Scale (FAS) [34] was completed at baseline, and at 6 and 12 months follow-up. The FAS is a 10-item self-report fatigue questionnaire. In addition to the total fatigue score, the FAS can be divided into a mental fatigue score and a physical fatigue score. The response scale is a five-point scale (1 never to 5 always); scores on the FAS can range from 10 to 50. The reliability and validity of the FAS appeared to be good in sarcoidosis patients [34,35].

2.6. Statistical procedure

In order to test the conceptual model presented in Fig. 1, structural equation modeling (SEM) analyses were performed using AMOS. The dependent variable FAS at 12 months was regressed on the explanatory variables of stressors (depressive symptoms, symptoms suggesting SFN, and dyspnea) and social support. An additional model was regressed at 6 months follow-up.

In the present study, 3% of the total number of values were missing, and 60 (19%) patients had missing data on at least one of the variables. A missing values analysis was performed to test whether the missing variables were Missing Completely At Random (MCAR). The little MCAR test was not significant ($\chi^2 = 119.88$, $df = 110$, $p = 0.25$), indicating that the missing data did not exhibit a systematic pattern. Subsequently, the data were analyzed by means of the AMOS software package 18.0 [26], which allows for the full information maximum likelihood (FIML) estimation of the model parameters when the data are incomplete.

A backward elimination strategy was used to achieve a parsimonious model. This elimination strategy was based on the evaluation of the critical ratio of the individual parameters, yielded by AMOS. The critical ratio for a parameter is estimated by dividing the estimated value by its standard error. Independent variables in the model were retained when the absolute value of their critical ratio was larger than 2.0. This critical ratio equals a significance test at the 5% level. The following fit indices were reported: Chi-Square goodness-of-fit (CMIN), comparative fit index (CFI), Tucker–Lewis index (TLI), and root-mean-square error of approximation (RMSEA) [36,37]. Values for CFI and TLI of 0.90 represents a good fit, while 0.95 represents an excellent fit [36,38]. RMSEA values of 0.05 indicate a close fit, 0.08 a reasonable fit, and 0.10 a poor fit [39].

3. Results

Table 1 summarizes the baseline characteristics of the participants of the present study. The mean fatigue score (FAS) at baseline was M = 29.6, SD = 8.4, while the mean fatigue score at 12 months follow-up was M = 30.1, SD = 7.7. Fifty-six patients did not complete the second survey mainly because they did not visit our outpatient clinic anymore and we lose contact. There was no difference in demographic or clinical data between both groups (data not shown). In the studied cohort 56 patients had a time since diagnosis ≤2 years. The mean FAS score of this subpopulation was 30.8 ± 9.8; median 32.5 (14–48). The other 236 had a mean FAS score of 29.2 ± 8.1; median 30.0 (10–46). This was not statistically different. The mean mental fatigue score at baseline was M = 12.7, SD = 4.4, while the mean mental fatigue score at 12 months follow-up was M = 13.7, SD = 4.2. The mean physical fatigue score at baseline was M = 16.7, SD = 4.6, while the mean physical fatigue score at 12 months follow-up was M = 16.5, SD = 4.2.

Of the studied sarcoidosis patients 52.1% had only pulmonary involvement and 47.9% had multiorgan involvement. The mean FAS of the subpopulation with pulmonary involvement was 29.1 ± 8.3 and of the subpopulation with multiorgan involvement 30.0 ± 8.6. There was no statistically difference.

Table 2 shows the correlation matrix between the baseline variables and fatigue at 12 months follow-up. All variables, except age and time since diagnosis, were related to fatigue. Everyday cognitive failure and

Table 1
Baseline characteristics.

	Participants (n = 292)
Demographics	
male	157 (53.8%)
age, years	48.3 ± 11.0
Medical variables	
time since diagnosis, years	8.1 ± 8.2
radiographic stages: 0/I/II/III/IV	130 (45%)/20 (7%)/65 (22%)/32 (11%)/43 (15%)
FVC, % predicted	99.4 ± 19.3
FEV_1, % predicted	89.9 ± 22.4
DLCO, % predicted	81.8 ± 17.9
pulmonary/multiorgan involvement, %	52.1/47.9
Medication	
prednisone[a]	95 (32.5%)
immunosuppressants[b]	54 (18.5%)
anti-TNF-α[c]	21 (7.2%)
pain killers	92 (31.5%)
antidepressants	20 (6.8%)
sleep medication	20 (6.8%)
Symptoms	
SFNSL score	24.6 ± 15.7
BDI score	2.6 ± 2.0
FAS score	29.5 ± 8.4
FAS mental score	12.7 ± 4.5
FAS physical score	16.7 ± 4.6
Psychological variables	
CESD score	14.1 ± 9.2
PSSS score	62.6 ± 13.4
STAI score	40.1 ± 10.2
CFQ score	37.5 ± 15.5

Data are presented as means ± standard deviation or in frequencies (percentages).
anti-TNF-α = anti-Tumor Necrosis Factor-alpha; BDI = Borg Dyspnea Index; CESD = Center for Epidemiological Studies-Depression Scale; CFQ = Cognitive Failure Questionnaire; DLCO = Diffuse capacity of the lung for carbon monoxide; FAS = Fatigue Assessment Scale; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; PSSS = Perceived Social Support Scale; SFNSL = Small Fiber Neuropathy Screenings List; STAI = State and Trait Anxiety Inventory.

[a] Prednisone (5–40 mg daily, orally).

[b] Methotrexate (5–15 mg once a week, orally, together with 5 mg folic acid once a week, orally); or azathioprine (50–100 mg daily, orally).

[c] Infliximab (5 mg/kg, every 4 weeks, intravenously) or adalimumab (40–80 mg once a week, subcutaneously).

Table 2
Pearson's correlations between variables at baseline and fatigue at follow-up.

	FAS score[a]	FAS mental score[a]	FAS physical score[a]
sex	−0.12*	−0.11	−0.11
age	−0.04	−0.02	−0.05
time since diagnosis	−0.03	−0.03	−0.03
BDI score	0.20**	0.17**	0.20**
STAI score	0.43**	0.44**	0.36**
PSSS score	−0.20**	−0.21**	−0.15**
SFNSL score	0.46**	0.39**	0.49**
CESD score	0.50**	0.51**	0.42**
CFQ score	0.53**	0.53**	0.45**

*$p < 0.05$;**$p < 0.01$.
BDI = Borg Dyspnea Index; CESD = Center for Epidemiological Studies-Depression Scale; CFQ = Cognitive Failure Questionnaire; FAS = Fatigue Assessment Scale; PSSS = Perceived Social Support Scale; SFNSL = Small Fiber Neuropathy Screenings List; STAI = State and Trait Anxiety Inventory.
[a] At 12 months follow-up.

depressive symptoms were strongly related to mental fatigue and moderately related to physical fatigue. In contrast, symptoms suggestive of SFN were more strongly related to physical fatigue and moderately related to mental fatigue.

In a first analysis, the initial conceptual path model as described in the Methods section yielded an acceptable fit. The value of the test statistic CMIN was 23.24, with 11° of freedom ($p = 0.02$). The results revealed that the absolute values of the critical ratios of 15 of the 26 path coefficients were smaller than 2.0. Removing these parameters one by one yielded a second, reduced model with a better fit: the value of CMIN was 33.84, with 25° of freedom ($p = 0.11$). The remaining 12 parameters in this model all had critical ratios with an absolute value larger than 2.0. Hence, this reduced model could not be simplified further without worsening the fit.

The path analyses yielded good fit indices: TLI = 0.97, CFI = 0.99, and RMSEA = 0.04 (CI 0.00–0.06). The model explained 37% of the variance in fatigue.

The statistically significant path coefficients are presented in Fig. 2. Patients who reported high levels of cognitive failure ($\beta = 0.31$), depressive symptoms ($\beta = 0.26$), symptoms suggesting SFN ($\beta = 0.16$), and dyspnea ($\beta = 0.10$) also reported high levels of fatigue. Fatigue was not predicted by time since diagnosis, sex, age, social support, or trait anxiety. Regarding the background variables, only age predicted dyspnea and cognitive failure. Older patients were more likely to report dyspnea ($\beta = 0.12$) than younger ones, and younger patients were more likely to report cognitive failure ($\beta = -0.12$) than older ones. In addition, sex predicted symptoms suggestive of SFN and cognitive failure. The women reported more symptoms suggestive of SFN ($\beta = -0.16$), and more cognitive failure (β = -0.16) than the men. Time since diagnosis was not predictive of any of the variables in the model. Trait anxiety predicted more cognitive failure ($\beta = 0.48$), more depressive symptoms ($\beta = 0.81$), less social support, ($\beta = -0.34$), and more symptoms suggesting SFN ($\beta = 0.32$), but not dyspnea.

When the path analyses were repeated with fatigue at 6 months, similar results were obtained. The fit indices at 6 months were good: CMIN = 36.75, $df = 25$, $p = 0.06$, TLI = 0.96, CFI = 0.98, and RMSEA = 0.04 (CI 0.00–0.07). This model explained 36% of the variance in fatigue at 6 months. The FAS score at 6 months correlated substantially with the FAS at 12 months (r = 0.78, common variance 50%).

4. Discussion

To the best of our knowledge, this is the first study to develop and test a conceptual model of fatigue in sarcoidosis in a longitudinal design. This model appeared to validly explain variation in fatigue. All tested symptoms (everyday cognitive failure, symptoms suggestive of SFN, depressive symptoms, and dyspnea) appeared to be significant predictors of fatigue at 12 months after the first evaluation of fatigue. The same model was valid for the prediction of fatigue at 6 months follow-up, which may partly be due to the fact that the FAS score at 6 months correlated substantially with the FAS at 12 months. Nonetheless, it indicates that the tested model remained stable over time. Everyday cognitive failure and depressive symptoms were the most important predictors of high levels of fatigue. Background variables (time since diagnosis, sex, and age), social support, and trait anxiety appeared not to predict fatigue. The negative associations between everyday cognitive failure, depressive symptoms, symptoms suggestive of SFN, dyspnea, and fatigue are in accordance with the findings of previous studies that also examined fatigue in sarcoidosis, although none of these studies had a longitudinal design or included all of these aspects [10,21,40,41].

In general, sarcoidosis patients turn out to be disabled with functional impairments due to sarcoidosis-associated symptoms, especially fatigue. Functional impairments are defined as limitations in, or inability to perform, certain physical activities, such as walking and lifting, or mental activities such as concentrating and conflict handling. Hence, functional impairments can be distinguished from symptoms (such as pain and fatigue), activity limitations (such as self-care tasks and gardening) and participation restrictions (such as leisure time activities and work). The most promising approach would appear to be to gather information using instruments such as questionnaires, performance tests or interviews, interpreted and assessed by physicians [42].

Consequences of cognitive impairment for the patient can be discomfort, such as memory problems and problems with attention and concentration [43] and affect self-management. Insight in cognitive functioning is of great importance in order to optimise self-management skills of patients with sarcoidosis. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment. The relationship between everyday cognitive failure and fatigue is in line with a previous study, which showed that patients with high levels of cognitive failure also reported higher levels of fatigue, compared to those with lower levels of cognitive failure [12]. The neuropsychological assessment for cognitive dysfunctions was restricted to a rather global and subjective screening instrument the CFQ. Labelling oneself as absent-minded or forgetful depends upon the perceived discrepancy between the subject's everyday memory functioning and her or his everyday memory demands. No substantial relationship was found with disease presentation, severity or duration. Self-reported cognitive changes or decline do not necessarily reflect actual cognitive decline. Beliefs about cognitive changes are strongly influenced by self-efficacy beliefs, personality, vitality and coping styles. Nevertheless, it seems unlikely that the favourable effect on cognitive functioning reported by patients, who were treated with anti-TNF-α drugs, is attributable to the use of a subjective screening instrument. In turn, patients with sarcoidosis often report everyday cognitive deficits [12]. Functional cognitive impairment, if present, may lead to increased fatigue and low compliance with medical treatment. Currently, however, no data are available on the extent of cognitive under performance among sarcoidosis patients. In a pilot study by our group standard neuropsychological tests were used to assess the cognitive domains of memory sensorimotor speed and information processing speed and cognitive flexibility. Only a small number of sarcoidosis patients (n = 27; 63% female; age 47.2 ± 10.8 years) were tested and compared with healthy controls. It was found that cognitive failure did not imply cognitive impairment (unpublished data). Thus subjective failure was not associated with cognitive impairment.

Research in multiple sclerosis patients found that memory complaints were not associated with memory performance, but were associated with fatigue complaints [19]. Functional cognitive impairment, if present, may lead to increased fatigue and low compliance with medical treatment. It is tempting to speculate that this may also be the case in sarcoidosis patients. An alternative explanation is that patients

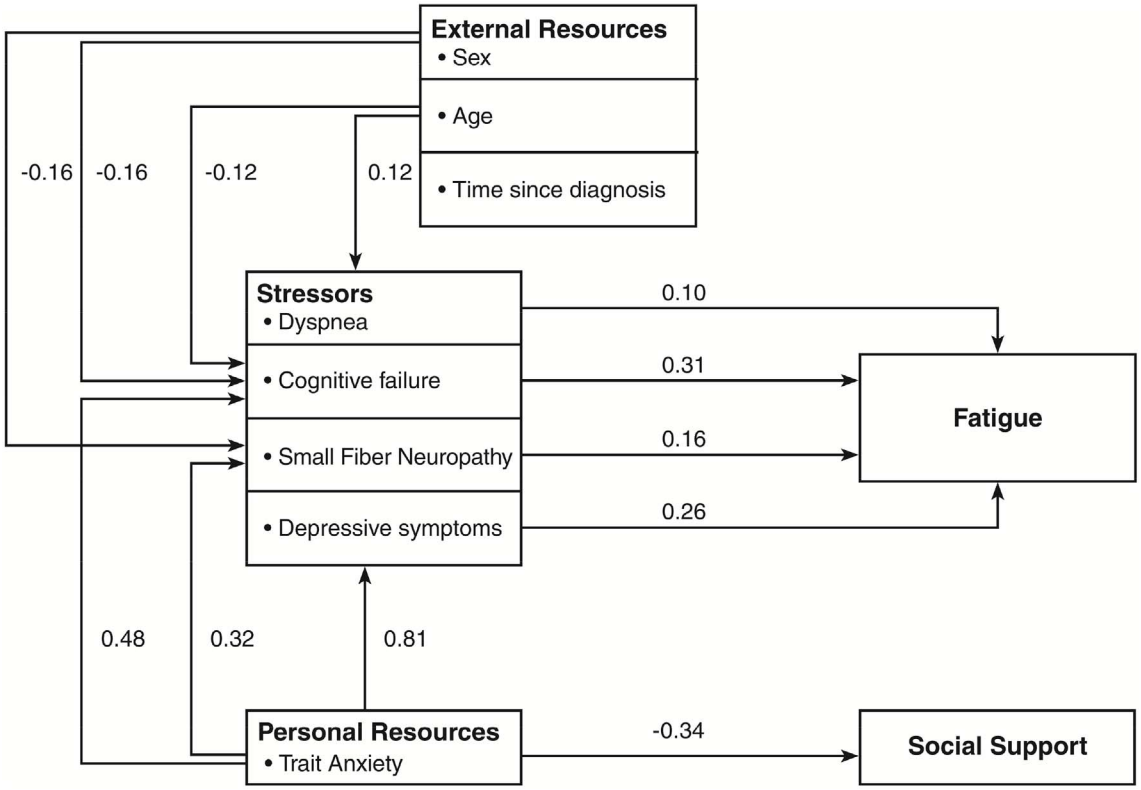

Fig. 2. Model that was tested to understand the associations between sex, age, time since diagnosis, social support, cognitive failure, depressive symptoms, dyspnea, small fiber neuropathy, and fatigue in sarcoidosis.[a]

[a] Error terms are omitted from this figure. Significant path coefficients are presented as standardized estimates. Sex is a categorical variable (0 = female, 1 = male). All predictors were measured at baseline, and fatigue at 12 months follow-up.

who experience more cognitive failures are continuously putting more cognitive effort into daily tasks (compensation) and consequently become more tired. This would be most strongly expressed in mental fatigue and to a lesser extent in physical fatigue, as we found in our correlational data.

Depressive symptoms and anxiety in sarcoidosis are at least partly an expression of exhaustion owing to the ongoing disease, and these psychological symptoms indeed play an important role in sarcoidosis [44–48]. They have been reported in 17%–66% of patients with sarcoidosis. Bosse-Henck et al. found that depression and anxiety were predictors of the development of severe fatigue [41]. In line with other studies, we found that depressive symptoms were negatively associated with, and affected, patients' fatigue scores, especially mental fatigue [10]. In addition, the relationship between fatigue and depressive symptoms parallels the findings for other chronic illnesses, such as diabetes, chronic obstructive pulmonary disease, cardiac disease, and rheumatoid arthritis [49]. Stepanski et al. [50] examined fatigue in patients with cancer, also by means of path analysis. In agreement with our results, they showed that depressive symptoms were related to fatigue. Moreover, anxiety and depressive and SFN-related symptoms in sarcoidosis are moderated by the severity and nature of fatigue. Fatigue and autonomic dysfunction are both dominant symptoms and risk factors for depression [51]. Anxiety consists of physical or hyperarousal symptoms, such as increased heart rate, perspiration, and dizziness, which are inherent to the reaction of the sympathetic nervous system [52]. In addition to a physical component, anxiety also has a cognitive component, that is, a thought (or chain of thoughts) that determines the emotion experienced. Anxiety is a major problem in sarcoidosis patients. Since fatigue is a symptom that is known to co-occur with anxiety, it is not surprising that anxiety in general and trait anxiety in particular were found to be related to fatigue [3,18,53]. In line with a previous study, we found that trait anxiety predicted fatigue at follow-up [53]. Studies of the relation between anxiety and dyspnea reported inconsistent results [54,55].

The nature of fatigue moderates the relationships between fatigue and everyday cognitive failure, depressive symptoms, and anxiety in sarcoidosis. The symptoms may share several neurobiological abnormalities, e.g., an increase in tumor necrosis factor alpha [2,51]. The relationship between depressive symptoms and fatigue may also be based on a cytokine imbalance, induced by an inflammatory immune response in sarcoidosis [49,56]. The cytokine balance of patients suffering from depression also seems to be disturbed [57]. However, understanding the nature of the relationships between fatigue, depressive symptoms, and anxiety remains difficult [58].

Research evidence suggests that the relationship between depressive symptoms and the severity of medical illness is bidirectional. Depressive symptoms may indirectly lead to increased symptoms, as depressive symptoms are associated with poor self-care (diet, exercise, giving up smoking, medication regimens) in patients with chronic diseases. Moreover, the presence of depressive symptoms is a mediator of the relationship between trait anxiety and fatigue. However, physical symptoms and the resulting functional impairments caused by complications of medical illness are also likely to impose a burden on the patient's life and provoke depression [49]. In the current study, the mean time since diagnosis was eight years. This indicates that most patients were chronically ill, and the functional impairments associated with sarcoidosis may also increase depressive symptoms.

Symptoms of SFN are disabling for patients, have a high impact on QoL, and are often difficult to treat [59,60]. Damage to or loss of small somatic nerve fibers results in pain, burning or tingling sensations, or numbness, typically affecting the limbs in a distal to proximal gradient. When autonomic fibers are affected, patients may experience restless legs, dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, or symptoms relating to autonomic

cardiac dysfunction. So far, a golden standard for the diagnosis of SFN is lacking [60]. We used temperature threshold testing (TTT) to diagnose SFN in the development of the SFNSL [61]. In the present study 19.2% of the patients had a SFNSL score < 11 (no signs of SFN); 34.2 had a score of 11–24; 25.8 of 37–48 and 8.8 a score of > 48 (indicating SFN). Of those who had a SFNSL score > 11 72.2% had an abnormal TTT.

In contrast to everyday cognitive failure and depressive symptoms, symptoms suggestive of SFN as assessed by the SFNSL [28] were found to be related to physical fatigue and only moderately related to mental fatigue. As regards the effect of the restless legs syndrome, the disturbance of sleep stages and sleep fragmentation, leading to daytime somnolence and fatigue, might offer an explanation for the greater fatigue in patients with this syndrome [6,24].

Fatigue was not predicted by social support, time since diagnosis, sex, or age. The absence of an association between time since diagnosis and fatigue is in agreement with previous studies [6,62], which reported that fatigue does not resolve spontaneously over time [63]. Regarding social support, Michielsen et al. [64] also failed to demonstrate an association between fatigue and social relationships in a healthy working population. Physical symptoms and the resulting functional impairments, as well as fatigue caused by complications of medical illness, are likely to impose a burden on the patient's life and to provoke everyday cognitive failure and depression [15,49]. The question of whether the burden or localization of the disease contributes to fatigue levels is highly interesting. It has been shown that patients with pulmonary and extrapulmonary sarcoidosis report higher fatigue levels than those in whom only the lungs are affected [6,65]. This suggests a possible additive effect for the symptom of fatigue.

We conclude that not only fatigue, but also everyday cognitive functioning, depressive symptoms, and anxiety, should be an integral part of the multidisciplinary management of sarcoidosis patients. From this perspective, various researchers have rightly suggested that sarcoidosis patients may benefit from psychological interventions [53,66] focusing on coping and appraisal, such as stress reduction therapy [23,67]. In any case, the basis for the interventions should be a type of cognitive-behavioral therapy, including so-called third-generation cognitive-behavioral therapy-like mindfulness-based cognitive therapy, as this type of therapy has proved to be effective in patients with anxiety disorder. Finally, it is important to realize that anxiety (just like depressive symptoms) is known to be among the factors sustaining fatigue, and that chronic fatigue can be successfully treated with cognitive–behavioral therapy.

A concern may be that this study was done in a sarcoidosis population of a sarcoidosis referral center in the Netherlands. However, also patients without functional impairment, for instance respiratory functional impairment and a time since diagnosis less than two years were included in this study. Often patients were referred because of very disabling fatigue without any functional impairment. There was no difference between the mean FAS score between those patients with or without respiratory functional impairment.

A limitation of the study may be that potential unknown predictors are missing. In post-cancer fatigue several fatigue persistent factors were identified: insufficient coping, anxiety, dysfunctional cognitions concerning fatigue, dysregulation of sleep, dysregulation of activity, and low social support and negative social interactions. In patients with chronic fatigue syndrome (CFS) sleep, anxiety, depressive symptoms or depression, personality (e.g., perfectionism), work, and education level were identified [68]. One could argue that sarcoidosis-associated fatigue resembles post-cancer fatigue, where the persisting factors play a major role. One could also argue that sarcoidosis-associated fatigue is chronic and that, therefore, the same persisting factors may play a role as in CFS. In the present study the assessed factors are also sustaining factors that indeed predict fatigue. We did not assess the persistent factors perfectionism and sleep, for instance, but these factors may also play a role in sarcoidosis-associated fatigue. Thus, identifying risk factors associated with symptom persistence is essential in improving treatment for patients with sarcoidosis-associated fatigue. Brooks et al. have provided an interesting rationale [69]. They have suggested that a more pessimistic view of the illness may encourage symptom focusing, which in turn may lead to the perpetuation of fatigue. How other factors play a part in this is yet unknown, but common sense leads us to suggest that the perpetuation of fatigue should in part be aimed at changing the perception of health complaints. In other words, coping with fatigue may be an important factor as well that was not assessed.

5. Conclusion

Everyday cognitive failure, depressive symptoms, symptoms suggestive of small fiber neuropathy, and to a lesser extent dyspnea, appeared to be significant predictors of fatigue 12 months after baseline. Therefore, in the management of sarcoidosis patients with fatigue and low energy levels we recommend to focus on an increased burden of concomitant symptoms. Since fatigue usually has a multifactorial cause, risk factors should also be examined and treated in combination. Future research involving more comprehensive neuropsychological batteries is warranted to investigate psychological functioning and fatigue in sarcoidosis. In addition, further research should give more attention to possible mediating or confounding pathways and associations between fatigue and everyday cognitive functioning, depressive symptoms, and SFN-related symptoms.

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Conflicts of interest

The authors who took part in this study declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. All authors read and approved the final manuscript.

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