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Sleep disturbance and symptom burden in sarcoidosis

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ABSTRACT

Introduction: Sarcoidosis is a systemic inflammatory disease associated with myriad symptoms, including fatigue. It can affect physiological processes like sleep, leading to poor sleep quality and excessive daytime sleepiness. We hypothesized that sarcoidosis patients would report more severe sleep disturbance than healthy controls and that relationships would be found with sleep disturbance and the severity of other symptoms.

Methods: We enrolled 84 sarcoidosis patients and 30 healthy controls and recorded demographic and clinical characteristics. Self-report measures were used to assess sleep disturbance, psychosocial symptoms, and quality of life at enrollment and longitudinally. Relationships between different self-report outcomes were analyzed using correlation statistics.

Results: Using the General Sleep Disturbance Scale, 54% of sarcoidosis patients reported frequent and occasional sleep disturbance compared to only 17% of healthy controls ($p < 0.0001$). This significant increase in sleep disturbance found in sarcoidosis patients strongly correlated with multiple psychosocial symptoms, including fatigue, depression, and cognitive dysfunction, and negatively impacted quality of life ($p < 0.01$). Traditional measures of sarcoidosis disease severity or activity were not associated with sleep disturbance. Sleep disturbance scores remained stable at follow-up (mean time between first and last administration of questionnaire was 17.3 months) in 56 of the sarcoidosis patients.

Conclusions: Sarcoidosis patients experienced significant sleep disturbance that correlated with higher levels of fatigue, depression, and cognitive dysfunction, and poorer quality of life. These associations were present regardless of disease severity or activity and result in decrements in quality of life and mental health.

1. Introduction

Sarcoidosis is an inflammatory disease of unknown etiology characterized by granulomatous inflammation [1]. As a systemic disease, granulomas can develop in any organ of the body causing significant variability in the type and degree of presenting symptoms [2]. Myriad constitutional symptoms may be reported, including fatigue, which is the most common one [3], and has detrimental effects on quality of life [4–6].

Sarcoidosis can result in sleep-related disorders [7–12]. For example, a higher prevalence of obstructive sleep apnea (OSA) occurs in sarcoidosis patients compared to healthy controls [11,13]. Sarcoidosis patients with OSA and parenchymal lung involvement also have higher apnea hypopnea and oxygen desaturation indices [13]. Additionally, periodic limb movements of sleep and restless legs syndrome occur in 41%–52% of sarcoidosis patients, respectively [12]. Sarcoidosis is also an independent predictor of excessive daytime sleepiness when controlling for other variables like OSA [8].

Multiple mechanisms may lead to sleep disorders in sarcoidosis. Respiratory symptoms associated with pulmonary sarcoidosis, the most common disease manifestation [2], may decrease sleep quality. Granulomatous inflammation of the upper airway may directly lead to sleep disturbance [10,14] or work in concert with weight gain from corticosteroids to induce OSA [11,15]. Sarcoidosis may manifest in the central nervous system as neurosarcoidosis, including direct infiltration of the hypothalamus, which is involved in regulating sleep and circadian function [9,16].

Although these collective data identified that sleep disorders appear to be prevalent in sarcoidosis patients, the impact of sarcoidosis on a patient's experience of sleep quality is unknown. We hypothesized that compared to healthy controls, patients with sarcoidosis would report higher levels of sleep disturbance. In addition, we evaluated the

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Abbreviations

Analysis of Variance ANOVA
Diffusing Capacity of the Lungs for Carbon Monoxide DLCO
Forced Expiratory Volume in 1 Second FEV1
Forced Vital Capacity FVC
General Sleep Disturbance Scale GSDS
Multiple Sclerosis Neuropsychology Screening Questionnaire MSNQ
Obstructive Sleep Apnea OSA
Patient Health Questionnaire PHQ9
Patient Reported Outcomes Measurement Information Systems PROMIS
Sleep Disturbance Score SDS
12-Item Short Form Health Survey SF-12

relationship between sleep disturbance and the severity of fatigue, depression, and neuropsychological function. We also assessed the impact of sleep disturbance on quality of life, and the relationship between sleep disturbance and traditional clinical measures of sarcoidosis inflammation. Through these analyses, we seek to further understand the relationship of sleep disturbance with other self-report outcomes in sarcoidosis.

2. Materials and methods

2.1. Cohort development and enrollment

Sarcoidosis patients and healthy controls were recruited from January 2010 through December 2015 as previously described [17] to participate in the University of California, San Francisco (UCSF) Sarcoidosis Research Program. Participants provided written informed consent. The study was approved by the UCSF Institutional Review Board.

A sarcoidosis diagnosis was confirmed according to accepted criteria using clinical features, exclusion of alternative diagnoses, and histopathological presence of non-necrotizing granulomas from biopsied organs [1]. Patients were excluded as described previously [18] for other disease processes that could contribute to sleep disturbance, including cancer, chronic infections, autoimmune diseases, or other pulmonary diseases. Available medical records from each patient were reviewed by sarcoidosis experts to assess organ involvement and Scadding stage, as previously described [19]. At each visit, spirometry and blood analysis was performed (HDpft 1000; nSpire, Longmont, CO, USA) [20]. All participants were evaluated at 6–12 month intervals for a duration of up to 60 months. Surveys were administered along with blood sampling. For this analysis, both cross-sectional and longitudinal data are presented as indicated.

2.2. Instruments

At each study visit, patients self-reported medication use, including sleep aids (including anti-histamines, anti-depressants, anti-convulsants, muscle relaxants, narcotics, melatonin, and sedatives). Both psychosocial symptoms and quality of life were evaluated using valid and reliable measures including: General Sleep Disturbance scale (GSDS) [21] to evaluate sleep; Patient Health Questionnaire (PHQ9) [22,23] to evaluate depression; the Patient Reported Outcomes Measurement Information Systems (PROMIS) [24] and Fatigue Assessment Scale (FAS) [25] to evaluate fatigue; the Multiple Sclerosis Neuropsychology Screening Questionnaire (MSNQ) [26,27] to evaluate neuropsychological function; and the 12-Item Short Form Health Survey (SF-12) [28,29] to evaluate quality of life.

The GSDS is a 21-item questionnaire that uses the sum of points (0–7 points per question), referred to as the “sleep disturbance score”, to define four groups: no disturbance (0–21 points), rare disturbance (22–42 points), occasional disturbance (43–63), and frequent disturbance (64 + points) [21]. The GSDS instrument was internally

Table 1
Demographics and clinical characteristics.

	Sarcoidosis		Healthy Controls		P-value
	N = 84		N = 30		
Gender	Female	Male	Female	Male	0.89
	46	38	16	14	
Race/Ethnicity					0.46
African-American[a]	8	1	2	2	
White Non-Hispanic[a]	33	30	9	10	
Hispanic[a]	2	3	3	1	
Asian/mixed other[a]	3	4	2	1	
Age (mean ± SD)	57 ± 10	49 ± 10	56 ± 10	50 ± 16	NS[b]
Body mass index (mean ± SD)	28 ± 6	30 ± 5	25 ± 3	26 ± 4	< 0.01
Reported Snoring	61		10		0.00014
OSA Diagnosis	11		0		–
Duration of Diagnosis (months)[c]	94 ± 88		–		–
Scadding Stage (0/I/II/III/IV)	10/12/40/7/15		–		–
Medications					
Any immunosuppressive[a]	48		0		–
Prednisone[a]	30		0		–
Opioids[a]	3		1		–
Benzodiazepines[a]	3		2		–
Any sleep-related medication[a]	32		8		0.26

OSA, obstructive sleep apnea.
Statically significant comparisons = four group comparisons between male and female sarcoidosis and healthy control subjects; and two group comparisons between sarcoidosis and healthy control subjects.
[a] Number of subjects.
[b] NS, non-significant comparisons for male groups and similar finding for female groups.
[c] Defined as time in months since biopsy to confirm the sarcoidosis diagnosis.

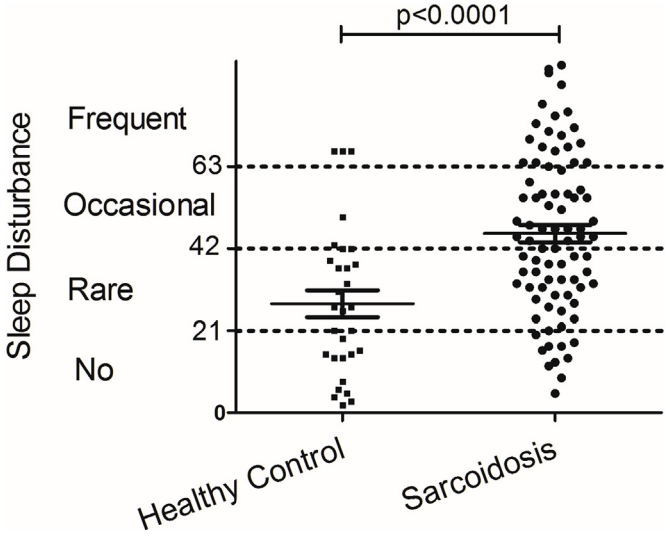

Fig. 1. Statistically significantly higher sleep disturbance scores measured by the General Sleep Disturbance Scale in sarcoidosis patients compared to healthy controls. The survey consists of 21-questions which are scored from 0 (meaning "never") to 7 ("every day") and the sum of scores is plotted as the y-axis. Dotted horizontal lines indicate the range of scores that fall into four discrete frequencies of sleep disturbance, "frequent, occasional, rare, and no." Data are presented as mean ± SEM; $p < 0.0001$; N = 84 sarcoidosis patients and 30 healthy controls.

consistent (Cronbach's alpha reliability coefficient = 0.91) in our two study groups. Although this scale has not been previously published in conjunction with sarcoidosis research, this scale was deemed favorable as it includes more domains to measure sleep quantity and quality compared to the Pittsburgh Sleep Quality Index [30], and it contains clinically meaningful cutoff scores. For example, a mean score of 3 across the 21 questions of the GSDS is considered clinically significant for sleep disturbance according to the Diagnostic and Statistical Manual of Mental Disorders [31]. Finally, the GSDS is validated in healthy individuals [21,32,33] and in patients with chronic disease (specifically, cancer, Parkinson's disease, and people living with HIV) [34–37].

The PHQ9 is a 9-item scale used to both diagnose and assess the severity of depression. It uses the sum of points (0–3 per item) to categorize participants as having minimal (0–4 points), mild (5–9 points), moderate (10–14 points), moderate-severe (15–19 points), or severe depression (20–27 points) [22]. The PHQ9 has well-established validity and reliability in the general population [23].

Fatigue was assessed using two different instruments. FAS is a 10-item patient reported outcome questionnaire that has demonstrated validity in the general population and in several different cohorts of sarcoidosis patients [25]. The 10-item PROMIS questionnaire is a valid and reliable measure to assess fatigue in sarcoidosis patients [24,38]. Each item is rated on a "Never" (1 point) to "Always" (5 points) scale. Both instruments dichotomize subjects into either experiencing or not experiencing fatigue (FAS: ≥21 points, PROMIS: ≥18 points).

MSNQ is a 15-item instrument developed in subjects with multiple sclerosis that assesses self-reported perception of cognitive deficits [27]. Items are scored on a 0 (Never, does not occur) to 4 (Very often, very disruptive) point scale. The total score dichotomizes participants into "cognitively impaired" (> 23 points) or "not cognitively impaired (0–23 points) [26,39].

SF-12 is an extensively used quality of life assessment tool that is scored into a Mental Component Summary (MCS) score and a Physical Component Summary (PCS) score [28]. The 12-item form combines several different formats, including dichotomized "Yes" or "No" answers and scales that rate the frequency and severity of emotional responses and physical abilities [29]. Higher scores indicate better quality of life in each category. The SF-12 is validated across several different adult cohorts in the US and internationally with a score of 50 considered a normative value for the US population [40,41].

2.3. Statistical analysis

Differences between the patients and healthy controls were assessed using Chi-square analyses and Fisher's Exact test. Continuous variables were tested for normality by the Shapiro-Wilke test. Non-parametric, two group comparisons were performed using the Mann-Whitney *U* test. For multiple groups comparisons, one-way analysis of variance (ANOVA) or Kruskal-Wallis tests were used for parametric or non-parametric data, respectively. Relationships were assessed using Pearson or Spearman correlations for parametric or non-parametric data, respectively. Analyses were performed using GraphPad PRISM V5 software (La Jolla, California, USA). A p value of < 0.05 was considered statistically significant.

3. Results

3.1. Demographics and cohort characteristics

Cross-sectional data were collected from 84 sarcoidosis patients and 30 healthy controls (Table 1). A similar distribution for sex, race, and ethnicity were seen between both groups. Sarcoidosis patients had a higher BMI and were more likely to report snoring than healthy controls. While eleven patients with sarcoidosis had a diagnosis of OSA, none of the healthy controls reported this diagnosis. Immunosuppressive medications were used only by sarcoidosis patients, with prednisone being the most common medication.

3.2. Sleep disturbance assessment

Our primary goal was to evaluate differences in sleep disturbance between our sarcoidosis patients and healthy controls. As shown in Fig. 1, compared to healthy controls, a significantly higher percentage of sarcoidosis patients (17% versus 54%, respectively) experienced frequent and occasional sleep disturbance ($p < 0.0001$).

Of the 21 items on the GSDS, items related to quantity and quality of sleep were scored significantly higher in sarcoidosis patients compared to healthy controls (Table 2). No statistically significant differences were found between sarcoidosis patients' and healthy controls' responses to items related to use of prescribed or over the counter sleep

Table 2
Differences Between Sarcoidosis Patients and Healthy Controls in Severity Scores for Items on the General Sleep Disturbance Scale with a p value < 0.0005.

Item Number	Sarcoidosis (mean ± SD)	Healthy Controls (mean ± SD)	P-value
3: Wake up too early at end of sleep	3.29 ± 2.48	1.67 ± 1.94	0.0005
5: Sleep Poorly	3.24 ± 2.15	1.70 ± 1.82	0.0005
6: Feel sleepy during the day	3.67 ± 2.07	2.17 ± 1.62	0.0001
7: Struggle to stay awake during the day	2.34 ± 2.09	1.00 ± 1.29	0.0003
9: Feel tired or fatigued during the day	3.38 ± 2.17	1.48 ± 1.64	0.0001
13: Get too little sleep	3.95 ± 3.00	2.13 ± 2.18	0.0003
15: Fall asleep unscheduled	1.89 ± 1.86	0.733 ± 1.34	0.0005

Table 3
Longitudinal change in sleep disturbance score.

Longitudinal Change in Sleep Disturbance Score	Average time between visits (months)	Sarcoidosis (mean ± SD)	Healthy Controls (mean ± SD)	P-value
1st- 2nd study visit (n = 73)	11.5	0.57 ± 15.20	-.89 ± 7.51	0.57
1st- last study visit (n = 26)	21.1	0 ± 15.37	−2.53 ± 9.16	0.34

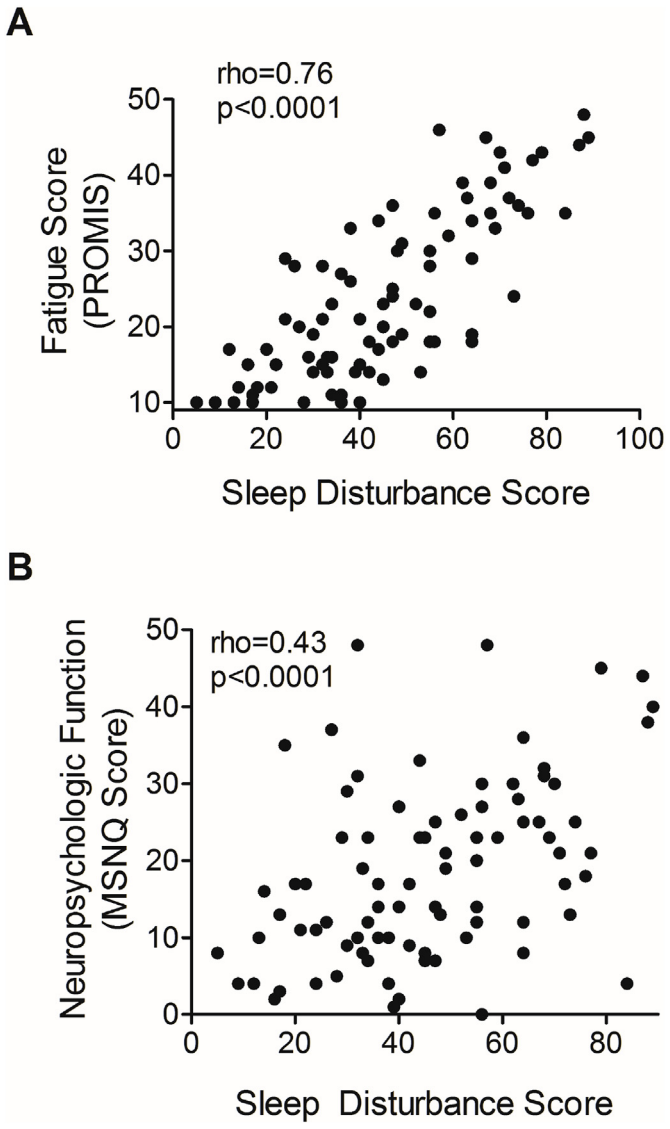

Fig. 2. Sleep disturbance was positively correlated with symptom-based surveys that assessed fatigue and neuropsychological dysfunction in sarcoidosis patients. A, Statistically significant correlation between fatigue measured by the Patient Reported Outcomes Measurement Information Systems (PROMIS) survey and the General Sleep Disturbance Scale (N = 84). B, Correlation between General Sleep Disturbance Scale and neurocognitive deficits as measured by the Multiple Sclerosis Neuropsychology Screening Questionnaire (MSNQ) (N = 84). Higher scores indicate greater self-reported fatigue and cognitive deficits, respectively.

aids or other substances to aid sleep. No significant changes in the total GSDS sleep disturbance score were found at approximately 1 year (mean 11.5 months) or 2 years (mean 21.1 months) of follow-up in sarcoidosis patients or healthy controls (Table 3).

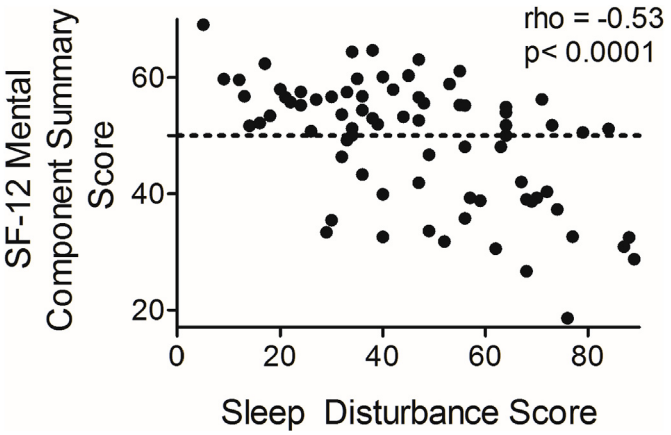

Fig. 3. Sleep Disturbance Score was negatively correlated with the Mental Component Summary score, as measured by the 12-Item Short Form Health Survey (SF-12) (N = 77). Dashed line indicates the normative value for the US population.

3.3. Correlations between sleep disturbance and physical and psychosocial symptoms in sarcoidosis

Significant positive correlations were found in the severity of sleep disturbance and fatigue as measured by both the PROMIS questionnaire (Fig. 2A; rho = 0.76, $p < 0.0001$) and the FAS questionnaire (Supplemental Fig. 1; rho = 0.62, $p < 0.0001$). In addition, a significant positive correlation was found between sleep disturbance score and self-reported cognitive deficits using the MSNQ (Fig. 2B; rho = 0.43, $p < 0.0001$). While we observed a strong correlation between sleep disturbance and the PHQ9 depression score (Supplemental Fig. 2, rho = 0.72, $p < 0.0001$), question number 3 of the PHQ9 elicits responses related to sleep ("trouble falling or staying asleep, or sleeping too much"). Removal of this question did not change the significant correlation between sleep disturbance score and depression score (rho = 0.67, $p < 0.0001$).

3.4. Correlations between sleep disturbance and quality of life in sarcoidosis patients

A majority (~70%) of sarcoidosis patients scored below the US normative value for the PSC of the SF-12 (Supplemental Fig. 3), and ~40% of sarcoidosis patients scored below the US normative value for MSC (Fig. 3). We found a significant negative correlation between the sleep disturbance score and the MCS score. In contrast, no correlation was found between the sleep disturbance score and the PCS score (Supplemental Fig. 3).

3.5. Assessment of other characteristics associated with poor sleep

The relationships between sleep disturbance and other known risk factors for sleep disturbance were evaluated. In sarcoidosis patients, we found no difference in sleep disturbance score for age, gender, body mass index, snoring, or blood pressure (Supplemental Figs. 4A–E).

In addition, associations between sleep disturbance and other factors that may affect sarcoidosis disease severity were examined. No differences were found in sleep disturbance score between sarcoidosis

patients when comparing use of immunosuppression, specific use of prednisone, or use of sleep aiding medications (Supplemental Figs. 5A–B). Similarly, sleep disturbance scores were not related to higher Scadding stage or longer disease duration, defined as the time from tissue biopsy confirming the diagnosis of sarcoidosis to the administration of the GSDS (Supplemental Figs. 6A–B). We found no relationship between sleep disturbance score and clinical disease activity, defined by a > 10% decrease in forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV1) or > 15% decrease in diffusing capacity of the lungs for carbon monoxide (DLCO) in pulmonary function testing measured over 36 months (Supplemental Fig. 7). In addition, lung function, defined as percent predicted for FVC, FEV1, and DLCO, did not correlate with sleep disturbance (data not shown).

4. Discussion

Many patients with sarcoidosis experience multiple physical and neuropsychological symptoms associated with their disease, like fatigue, depression, and perception of cognitive dysfunction. These symptoms are difficult to quantify in the clinic and often do not improve with treatment of sarcoidosis-associated inflammation. In this study, we explored the severity of sleep disturbance in sarcoidosis and examined how sleep disturbance relates to patient reported assessment of these physical and neuropsychological symptoms and traditional measures of disease severity. We identified a significant increase in sleep disturbance in sarcoidosis patients compared to healthy controls that strongly correlated with multiple psychosocial symptoms and negatively impacted quality of life. Interestingly, traditional measures of disease severity (e.g. pulmonary function measures and Scadding stage) were not associated with the severity of sleep disturbance. Taken together, these findings demonstrate a relationship between the quality and quantity of sleep in sarcoidosis patients and their experience of adverse symptoms in daily life, which we found to be independent of the clinical or radiographic assessment of disease duration, activity, and severity.

Using the GSDS sleep disturbance score, the majority of sarcoidosis patients experienced a clinically meaningful level of sleep disturbance (Fig. 1). This finding was contrasted with only a minority of healthy controls who experienced this severity of sleep disturbance. While we report the first use of the GSDS in sarcoidosis subjects, this questionnaire was internally consistent in our subjects, and it has been used in other systemic and pulmonary diseases including HIV [34] and lung cancer [42] to assess sleep. In a study of HIV patients who were dichotomized into having “no pain” or clinically significant “pain”, those with “pain” experienced a much greater degree of sleep disturbance compared to those with “no pain”. The amount of sleep disturbance experienced by HIV patients with “pain” in that study was similar to that experienced by sarcoidosis patients in our study. A recent prospective longitudinal study evaluated sleep disturbance in patients with lung cancer who were assessed before and after surgery found that ~60% of these patients experienced clinically meaningful sleep disturbance which did not improve significantly during the 12 month follow-up period [42]. The degree of sleep disturbance in this cohort of lung cancer patients was similar to what we observed in our sarcoidosis cohort. These findings from HIV and lung cancer patients serve as important comparisons to appreciate the severity of sleep disturbance in sarcoidosis, which will need to be validated in future studies.

We used the SF-12 to assess quality of life measures and in our cohort and found a negative correlation between the MCS and the sleep disturbance score while no relationship with sleep score and PCS was found (Fig. 3 and Supplemental Fig. 3). We were unable to find a prior study that assessed quality of life in relationship to sleep disturbance in sarcoidosis and therefore validation of these findings will be important. Since the MCS score reflects energy levels, social functioning, and psychological distress, while the PCS score reflects physical functioning, pain, and general health perceptions, our results suggest that greater levels of sleep disturbance are not significantly associated with greater impairments of a patient's physical functioning compared to impairments in the factors that make up the MCS score.

Poor sleep quality has been reported with sleep-disordered breathing and/or lung restriction [43]. In our prospective, longitudinal cohort, we found no correlation between quantitative measures of lung function or disease activity with increasing sleep disturbance score. Nor did we find differences in overall sleep disturbance when examining use of immunosuppressive medications, including prednisone, in our group of sarcoidosis patients. Risk factors for OSA, including age above 50 years old, male gender, and snoring, similarly had no definable impact on sleep disturbance scores in our sarcoidosis patients. However, sleep disturbance positively correlated with both fatigue and self-reported cognitive deficits (Fig. 2). These findings strongly point to the need to assess and to treat mental health and sleep disturbance in patients with sarcoidosis to prevent deterioration in quality of life and minimize symptom burden, regardless of disease severity or activity.

While our study benefits from its prospective, longitudinal design, it is limited by its sample size and reliance on data from one institution. The lack of formal screening for OSA in all subjects upon entry into the cohort may limit the applicability of our findings as there was a high self-reported rate of snoring in sarcoidosis subjects, which may imply undiagnosed sleep disordered breathing. Results of a prior study of polysomnography found less severe OSA in sarcoidosis patients compared to a non-sarcoidosis control group [8]. Collectively, these studies underscore the importance to formally characterize subjects' sleep physiology (e.g. sleep studies, actigraphy, sleep diaries) in relation to self-reported sleep disturbance in future studies. A comprehensive diagnostic approach will be necessary to determine whether sleep is truly disrupted in these patients by mechanisms such as OSA or whether self-reported sleep disturbance may relate to more complex neuropsychiatric perceptions of sleep and illness in sarcoidosis.

In summary, patients with sarcoidosis experience various symptoms that detrimentally affect their quality of life and mental health. Our study goals were to relate self-reported sleep disturbance, mental health, and cognitive function, with physical health and disease activity and severity. Our findings show a disparity in sleep disturbance between sarcoidosis patients and healthy controls, and reveal important relationships between sleep, emotional health, and quality of life in people with sarcoidosis. More investigation is needed to screen for causes of poor sleep, such as OSA, in sarcoidosis and whether improvements in sleep lead to improvements in quality of life measures.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2018.03.021.

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