RESPIRATORY CARE Paper in Press. Published on November 19, 2013 as DOI: 10.4187/respcare.02080

Factors associated with fatigue in sarcoidosis

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Conflict of Interest

Research was supported by the German Sarcoidosis Society.

Abstract

Background: Fatigue is a frequent symptom of patients suffering from sarcoidosis. The origin of fatigue associated with sarcoidosis is unclear. The aim of this study was to assess the impact of affected organs, medication, and comorbidity on fatigue related to sarcoidosis.

Method: In collaboration with the German Sarcoidosis Society, a sample of 1197 subjects, diagnosed with sarcoidosis, were examined. The participants completed a questionnaire that contained the Fatigue Assessment Scale (FAS) and the Multidimensional Fatigue Inventory (MFI).

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Results: In this study, muscles, bones and nerves were most strongly associated with fatigue. Patients receiving prednisolone showed heightened fatigue levels, however, the association between the duration of prednisolone therapy and fatigue was weak. The concomitant diseases, pulmonary hypertension and sleep apnoea, showed the greatest impact elevating fatigue (effect sizes d>0.50). In the combined regression analysis, comorbidity was the most important predictor of fatigue.

Conclusions: It is important to consider that multiple clinical factors, especially comorbidities, contribute to the high degrees of fatigue in sarcoidosis.

Key words: comorbidity, fatigue, organs, sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease. Although the disease may involve almost every organ of the body, the lung is predominantly affected. Patients suffer from a broad spectrum of symptoms. Frequently observed specific clinical features are shortness of breath, cough, and chest pain (pulmonary) [1], cranial nerve palsy (neurological), and erythema nodosum, maculopapular lesion or lupus pernio (dermatological) [1-3]. Non-specific symptoms are chronic fatigue, weight loss, night sweats, fever, or malaise [3-5].

Fatigue is one of the most common symptoms in sarcoidosis [6] and impairs the quality of life [7, 8]. In a previous study by this group, the level of fatigue within the same cohort with sarcoidosis was compared to general population. FAS and MFI fatigue scales were used. Sarcoidosis patients showed higher levels of fatigue with younger patients suffering to greater extent than older ones [9]. However, the reasons for higher levels of fatigue in patients with sarcoidosis are unknown. Clinical parameters show inconsistent correlation with elevated fatigue levels [10]. The affected organs might be of critical importance, since patients suffering from pulmonary and extrapulmonary disseminated sarcoidosis have higher fatigue levels than patients with pulmonary sarcoidosis [11].

Comorbidity may contribute to fatigue levels. Examples include restless legs syndrome, which leads to a disturbed and superficial sleep with subsequent fatigue, insomnia and daytime somnolence [12, 13]. Obstructive sleep apnoea (OSA) correlates with poorer quality of life with respect to sleep, fatigue and energy levels[14, 15]. Body mass index, BMI, has been proven to be an independent predictor of fatigue

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in OSA-Patients[15-17]. Metabolic and endocrinological disorders, e.g. diabetes mellitus and thyroid disorder, are also significantly associated with fatigue [18] and may play a role in the development of fatigue in patients suffering from sarcoidosis. Pulmonary Hypertension (pHT) is often observed in advanced sarcoidosis, and contributes to increased mortality and poor prognosis [19]. Patients with pHT have a significantly shorter 6-min walking distance and higher levels of fatigue than patients without pHT[20]. Further complicating conclusive analysis treatment options of sarcoidosis may themselves impact fatigue development. In particular, prednisolone has been shown to have a nearly linear correlation with sleeping problems[21].

Though there are several studies examining specific putative reasons for elevated fatigue levels in sarcoidosis, many of them are based on relative low sample sizes[22]. Furthermore, the association between comorbidity and fatigue has only been mentioned in case reports[23]. Hence, in the current study, we intended to comprehensively test several factors associated with fatigue in sarcoidosis.

Methods

Sample

The study was performed in collaboration with the German Sarcoidosis Society. In 2009, all members of the society (N=4100) were requested to complete a questionnaire concerning demographic characteristics, affected organs, medication, symptoms, and comorbidities. Fatigue was assessed with two standardized questionnaires (see questionnaire). The questionnaire was delivered to the members by post, with an accompanying letter, a consent form, and a return envelope. The response rate was 31%. A total of 73 questionnaires were excluded from analysis because the respondents wrote their names on the questionnaire (contradicting the pseudonymization procedure) and/or too many missing values. The final analysis was based on 1197 questionnaires. The study was reviewed and approved by the Ethics Committee of Leipzig University. In a previous study with the same sample of patients, the fatigue levels of the study participants were compared with those of the general populations, and age and gender differences were calculated

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Questionnaire

Regarding affected organs, 10 specific organs covering the most commonly affected sites were included in the questionnaire: lungs, heart, skin, muscle, nerves, eyes, bones, kidneys, lymphatic nodes, and liver and a category “other organs”. Participants were requested to indicate whether the organs were currently affected or not by checking on a box with either “yes” or “no”, multiple answers were possible. Medication was assessed with the same method. Medication categories were prednisolone, azathioprine, methotrexate, cyclophosphamide and oxygen, including the duration (in years) of prednisolone therapy. Participants were asked to state the present medication they are on. Comorbidity was assessed in the same way. The list included diabetes, congestive heart disease, thyroid dysfunction, sleep apnoea, restless legs syndrome, and pulmonary hypertension, and for each of the diseases the subjects had to indicate whether they suffered currently from the disease or not. In all evaluated items, participants had to indicate their present state not the past.

FAS

The Fatigue Assessment Scale, FAS, is the most frequently used fatigue questionnaire in sarcoidosis [22], [24]. Initially developed by Michielsen et al. (2004) [25], it is a well validated and reliable scale [22]. The questionnaire consists of two subscales, five questions concerning the physical and five questions concerning the mental aspect of fatigue. There are five answer options ranging from “never” to ”always”. An example for physical subscales is “I get tired very quickly.” A cut-off score of 22+ is a widely accepted criterion for elevated fatigue [25].

MFI

The Multidimensional Fatigue Inventory MFI was developed by Smets et al. 1995 [26]. This fatigue scale is widely used in cancer patients, patients with chronic fatigue syndrome and chronic inflammatory diseases [27-29]. It is well validated [29] with an internal consistency (Cronbach’s α) ranging from 0.79 to 0.93 [27].

MFI consists of five subscales: General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation, and Mental Fatigue, each subscale covering four items with five answer options (1 “yes, true” to 5 “no, not true”) each . A question, for example, would be “Thinking requires effort”. According to Kuhnt et al. 2009 [30], the 75th percentile (53+) was used as the cut-off value for high fatigue.

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Statistical analysis

Group differences in means values of fatigue scores were calculated with t-tests. Effect sizes d were calculated according to Cohen [31]. Cohen's d is a commonly used value to evaluate the magnitude of differences irrespective of the sample size. It is defined as the mean score difference of two groups, divided by the pooled standard deviation. For each organ category, the mean fatigue differences between subjects with and without affected organs were calculated, indicated as effect sizes d. Furthermore, the number of organ categories was calculated for each subject (mean: 2.1 organ categories) and participants with multiple affected organs (3 and more) were compared with participants with 1 or 2 affected organs.

Especially in studies with large number of participants, the effect size is a better measure than the significance level, because even small differences in mean values can reach significance simply due to sample size. A d value of 0.2 or less is interpreted as small, while a d value of 0.5 is classified as medium and 0.8 as a large effect. Significant differences do not necessarily render clinical important effects. Therefore, d values provide a better judgement concerning clinical importance of group differences. Several researchers consider an effect size of 0.5 (half standard deviation) clinically important [32]. According to this criterion, a FAS difference of 4 points and a MFI difference of 8 points is assumed to be clinically important since the FAS and MFI standard deviations are about 8 and 16, respectively. However, even smaller differences than d=0.50 may be relevant from an epidemiological point of view.

The hypothesized predicting factors of fatigue maybe interrelated. Since the inclusion of all single organs, medication and comorbidity would result in too many predictors for multivariate analyses, we restricted the analysis to the numbers of affected organs, medication and concomitant diseases, together with age and gender. Previous studies showed effects of age and gender on fatigue. Women generally report more fatigue than males. Therefore, age and gender were included in the multivariate analyses. Multiple regression analyses (method=enter) were performed to test the association between multiple predictors and the outcome (fatigue). Multiple R coefficients describe the correlation between the optimal linear combination of the predictors with the outcome. The regression coefficient "B" describes the predictive strength of the independent variable as follows: On average, the fatigue score (dependent variable) differed by X amount for every one unit increase in Y predictor, while keeping the others constant. "Beta" is the standardized partial regression coefficient, ranging between

-1.0 and 1.0. It can be interpreted as the correlation coefficient of the respective variable in the regression analysis with multiple predictors. All calculations were performed with SPSS version 17.0.

Results

The mean age of the study sample (N=1197) was 54.3 years (cf. Table 1), 65.4 % were females. In the Sarcoidosis Society, the mean age of all members was 55.9 years, and 60.0 % were females. Both questionnaires confirm high percentages of participants suffering from fatigue, mean fatigue scores are illustrated in Table 1. Females are more affected than males ($p<0.01$).

Affected organs

In Table 2, several univariate results of mean fatigue scores for each kind of affected organ are presented. The organs are arranged according to the frequency of affection.

The lungs were the most frequently reported site of manifestation of sarcoidosis (91%). To evaluate the impact of additional affected areas, the group of participants with pulmonary manifestation was divided into two subsamples: pulmonary alone and pulmonary plus extrapulmonary.

Both questionnaires yielded similar results in Table 2.The greatest differences were found for muscles, bones, and nerves, related to fatigue levels ($p<0.001$). The lungs, skin, lymph nodes, and eyes were the organs most reported to be affected by sarcoidosis and showed relatively small group mean differences in fatigue. Participants with three or more affected organs reported more fatigue (FAS: $d=0.39$; MFI: $d=0.31$) than participants with one or two affected organs ($p<0.001$). Extrapulmonary involvement in addition to pulmonary manifestation correlates with a higher fatigue level (FAS: $d=0.28$; MFI: $d=0.30$; $p<0.001$).

Medication

The relationship between medication and fatigue is displayed in Table 3.

Prednisolone was the predominant therapy (45.3%), followed by the immune modulator Azathioprine (5%), and Methotrexate (2.8%). All medication was associated with higher fatigue levels, with Methotrexate showing the greatest impact on fatigue (FAS: $d=0.44$, $p<0.01$; MFI: $d=0.42$, $p<0.05$). The mean duration of prednisolone therapy was 5.7 years.

Multi-drug treatment is possible. Most patients were on none (N=619) or one (N=578) medication. Patients receiving at least two medication (N=77) reported higher fatigue levels in FAS than those with 0 or 1 kind of medication.

Comorbidity

The frequencies of concomitant diseases were as follows (cf. Table 4): arterial hypertension (37.9%), thyroid disease (26.9%), obesity (26.7%), restless legs syndrome (15.7%), diabetes mellitus (11.2%), sleep apnoea (8.8%), and pulmonary hypertension (3.2%). All comorbidities were associated with higher fatigue levels (Table 4). Sleep apnoea and pulmonary hypertension were most strongly related to fatigue (d>0.50), followed by obesity and restless legs syndrome. Arterial hypertension, the most frequent concomitant disease, reaching effect sizes of d=0.19 (FAS) and d=0.28 (MFI), which is also statistically significant (p<0.01). 195 participants (16.3%) reported three or more comorbidities, and these participants reported highest fatigue values (FAS: d=0.45; MFI: d=0.57; p<0.001).

Multiple regression analyses

Affected organs, medication and comorbidity may be interrelated. In addition, these factors may be age and/or gender specific. The effects, therefore, given in Tables 2 to 4 may depend on these mutual relationships. Multiple regression analyses were used to test the independent statistical influence of the different factors on fatigue. Table 5 shows that the three components (affected organs, medication and comorbidity) significantly contributed to the prediction of fatigue. Comorbidity was most strongly associated with fatigue, with beta scores of about 0.20. The influence of gender on fatigue levels was statistically significant (higher fatigue scores for females compared to males), but only on the 5% level of variance.

While the FAS showed a significant age effect (p<0.001), the MFI failed to confirm that effect (p>0.05). The multiple R values of 0.28 and 0.29 correspond to an explained variance of about 8%. Sleep apnea and pulmonary hypertension were the conditions with the greatest effects on fatigue in the univariate analyses. To test these effects in a multivariate model, we also performed multivariate regression analyses with the predictors of table 5 combined with these two conditions (sleep apnea and pulmonary hypertension). The results for the MFI were: Sleep apnea: B=6.09, Beta=0.10, p=0.002; Pulmonary hypertension: B=7.14, Beta=0.07, p=0.014. The corresponding FAS coefficients were: Sleep apnea: B=3.94, Beta=0.14, p=0.001; Pulmonary hypertension: B=2.15, Beta=0.05; p=0.10.

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Discussion

In this study the association of fatigue in sarcoidosis patients concerning different manifestations sites, medication, and comorbidities has been studied. Level of fatigue was measured with MFI and FAS fatigue tests. It was found that patients with additional manifestation sites to pulmonary sarcoidosis have higher levels of fatigue than those with only pulmonary affliction. Furthermore, the comorbidity of pulmonary hypertension and sleep apnoea showed the greatest effects on fatigue in multivariate analysis. Patients who are on medication with prednisolone for sarcoidosis were significantly above the cut off values for MFI and FAS. However, these results were obtained in univariate analyses and may be, at least in part, due to confounding.

The question whether the burden or localisation of the disease contributes to fatigue levels is highly interesting. In a two way approach we initially identified the muscles, bones, and nerves to show the highest effect sizes in direct association. Surprisingly, these manifestations sites are not among the most afflicted, but the lungs for which also higher values in MFI and FAS could be found but with less effect size. Sarcoidosis induces inflammatory reactions, leading to the formation of granulomata and nonspecific reaction of tissue. In terms of the lungs the pathology of commonly complained increased fatigue [11] is not quite clear. Restrictive/ obstructive affliction or a reduction of diffusion capacity might be induced [33] by the disease, leading to lesser oxygenation of the blood and consecutive increase in fatigue.

Concerning non-pulmonary manifestation sites, sarcoidosis involvement of the musculoskeletal system may present as myalgia [4] or lytic bone lesions [34] leading to physical inactivity, lack of exercise, worsening of performance and deconditioning in physical capacity [35, 36]. Manifestation in the heart muscle may cause reduced myocardial contraction strength, blocks [37] or arrhythmias [38], resulting in a lower cardiac output, dyspnoea and fatigue. In so far, localization of sarcoidotic lesions plays an important role. With the strong association of extrapulmonary sarcoidotic manifestation it stood to reason to examine the additional effect of these manifestation sites to pulmonary affliction. It could be shown that those patients suffering from pulmonary and extrapulmonary sarcoidosis reported higher fatigue levels than those with only the lungs affected. This has also been shown by Gvozdenovic et al. [11] and suggests a possible additive effect to the symptom of fatigue. Furthermore, not only the localization but also the burden of the disease, seen as numbers of afflicted organs, have showed an

influence on the level of fatigue as patients with three or more organs afflicted reported significantly more fatigue than those with less than three organs afflicted.

Manifestation sites of the disease play not the only role as we found that certain comorbidities were also strongly associated in increased fatigue levels. Above all, sleep apnoea, occurring in 9% of the sample, showed the strongest effect sizes in direct association. Sleep apnoea is an interruption of sleep due to the collapse of upper airways, leading to hypoxic episodes. Possible causes might be constitutional reasons as obesity, laryngeal manifestation of sarcoidosis, and neurosarcoidosis. For sleep apnoe exists a well-documented association to higher BMI levels [39] which correlated with higher self-reported fatigue in our study. Interestingly, obesity and diabetes seem not only be associated via sleep apnoe with fatigue [17] but depicts independent influencing factor. As sleep apnoe causes hypoxic episodes, the fatigue due to obesity and diabetes might be mediated through psychological distress and elevated levels of interleukin 6, secreted by adipose cells [40].

Concerning the effect of restless legs, the disturbance of sleep stages and sleep fragmentation leading to daytime somnolence and fatigue might offer an explanation to greater fatigue in patients suffering from this syndrome. The most common reported comorbidity of arterial hypertension contributes little amount of fatigue levels. Interestingly, the impairment of the thyroid shows no impact on overall fatigue due to sarcoidosis, since the effect sizes of diseases of the thyroid gland on fatigue were low.

The relationship between *medication* and fatigue is comparable to that of the affected organs and fatigue. It is generally accepted that chemotherapy induces fatigue[41], however, the different compounds seem to have an interindividual association of variable strength. Different effects of prednisolone have been previously documented in the literature[25]. According to Drent et al. [4], prednisolone may induce muscle weakness, leading to a collapse of upper airway muscles and therefore yielding fatigue. Whether this direct effect of prednisolone increases the fatigue in patients with sarcoidosis or the higher activity of disease which makes the treatment with prednisolone necessary is not quite clear and should be considered in further investigations. The same is to be considered for the treatment with Methotrexate. As it is commonly used in escalating the therapy the different effects on fatigue are hardly to be kept apart.

The analysis of direct associations had yielded certain factors to be connected to the level of fatigue but some additional aspects for interpretation have to be considered. Affected organs can occur in

multiple combinations. The most frequent affected organ (lung) seems to have a negligible and non-significant association with fatigue, since patients with and without lung affection show similar fatigue levels. Here one must take into account that in the control group (patients without affection of the lungs) are more subjects with other sites of affection. Involvement of muscles, bones, and nerves are relatively uncommon (<10% prevalence each), compared to the respiratory system. For these organs, the d values in Table 2 are appropriate measures to indicate the strength of association, since the differences between the groups concerning the other organs are smaller. Therefore, it is also useful to calculate the number of affected organs. The same is true for concomitant diseases. Multiple combinations are possible. As in the analysis of affected organs, the most frequent concomitant diseases (hypertension and diseases of the thyroid gland) show lower effect sizes than the (rare) diseases pulmonary hypertension and sleep apnoea. The above mentioned problems of the univariate analyses (multiple combinations of affected organs, concomitant diseases and medication) call for a multivariate analysis. Table 5 shows that comorbidity is the most important independent factor (highest beta values) associated with fatigue. While sleep apnea was an independent factor even in the multivariate analyses, pulmonary hypertension failed to reach statistical significance in the multivariate context, though the univariate effect was also high. This may be due to the small prevalence (3 %) of pulmonary hypertension.

The *limitations* of this study should be acknowledged. The study was based on self-reported data and not on clinical examination. Furthermore, due to the voluntary participation in this study a response bias cannot be excluded. Selection bias can also be an additional source of errors. In our sample females were slightly overrepresented (65 % in the sample vs. 60 % in the society), but there were only small age differences between respondents and non-respondents. Therefore, concerning these demographic factors the sample can be assumed to be fairly representative of the members of the society, however, the society might not represent all patients suffering from fatigue. The correlations found in this study are of statistical matter. A two-step approach, first univariate correlations then multivariate correlations, was used to identify possible predictors of fatigue. The predictors found do not indicate causative relationships but describe statistical connections. The study includes multiple univariate statistical tests. Therefore, because of the problem of multiple testing some effects may be due to chance. As a consequence, we restrict the interpretation to those effects that occur in both questionnaires, with significance levels of 0.01. The rates of comorbidity correspond to those reported

in other studies. Finally, affected organs, treatment, comorbidity and age are interrelated. Tables 2 to 4 report univariate group differences. Combined analyses, taking into account certain combinations of affected organs or combinations of comorbidity provided a deeper insight in the predictors of fatigue. It might be useful to examine certain typical combinations of affected organs and comorbidity.

In conclusion, we reconfirm that fatigue is a major problem in patients suffering from sarcoidosis. Highest mean fatigue levels were reported from patients with sarcoidosis for muscles, bones, and nerves, whereas mere pulmonary sarcoidosis was associated with a lesser amount of fatigue. In addition, patients affected with pulmonary and extrapulmonary manifestation sites showed higher fatigue levels.

In terms of treatments, we found Prednisolone to be strongly associated with fatigue levels in patients with sarcoidosis, as well as Methotrexate. The same was found for the concomitant diseases of sleep apnoea and pulmonary hypertension. However, in the multivariate analysis only sleep apnoea showed a strong effect and should therefore be carefully considered and treated for.

The total burden of multiple affected organs in combination with the number of medication and concomitant disease was examined in an integrated approach. It is to be reckoned that an increase in the number of affected organs, an intensified therapy, and an increased burden of concomitant diseases is associated with increased fatigue levels.

Acknowledgement

This study was supported by the German Sarcoidosis Society (Deutsche Sarkoidosegesellschaft).

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RESPIRATORY CARE Paper in Press. Published on November 19, 2013 as DOI: 10.4187/respcare.02080

Table 1. Demographic characteristics and mean fatigue scores

	Total (N=1197) M ± SD	Males (N=414) M ± SD	Females (N=783) M ± SD
Demographic data			
Sex		34.6 %	65.4 %
Age (years)	54.3 ± 11.6	53.9 ± 10.9	54.5 ± 12.0
Fatigue data			
FAS mean score	26.3 ± 7.9	25.2 ± 8.4	26.8 ± 7.6
FAS % above cut-off 22+	69.7 %	62.1 %	73.7 %
MFI mean score	60.5 ± 17.2	58.0 ± 18.1	61.8 ± 16.5
MFI % above cut-off 53+	67.9 %	62.3 %	70.9 %

FAS: Fatigue Assessment Scale; MFI: Multidimensional Fatigue Inventory, M: Mean, SD: standard deviation, N: number of cases.

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Table 2. The association of affected organs and fatigue

			FAS			MFI		
Organs		N	M ± SD	d	p	M ± SD	d	p
Lungs	yes	1086	26.2 ± 7.9			60.5 ± 17.3		
	no	111	26.5 ± 7.4	0.04	n.s.	60.5 ± 15.9	0.00	n.s.
Skin	yes	293	26.1 ± 8.0			60.6 ± 16.7		
	no	904	26.6 ± 7.2	0.07	n.s.	61.1 ± 17.3	0.09	n.s.
Lymphatic nodes	yes	249	26.6 ± 7.8			61.1 ± 16.9		
	no	948	26.2 ± 7.9	0.05	n.s	60.3 ± 17.3	0.05	n.s.
Eyes	yes	191	26.7 ± 7.3			61.8 ± 17.1		
	no	1006	26.2 ± 7.9	0.07	n.s	60.2 ± 17.2	0.09	n.s
Liver	yes	141	28.1 ± 7.9			62.9 ± 17.5		
	no	1056	25.9 ± 7.8	0.28	< 0.05	60.1 ± 17.1	0.16	n.s.
Muscles	yes	113	29.9 ± 7.8			67.2 ± 15.4		
	no	1084	25.9 ± 7.8	0.51	< 0.001	59.8 ± 17.2	0.45	< 0.001
Nerves	yes	108	29.1 ± 8.4			65.6 ± 16.8		
	no	1089	25.9 ± 7.8	0.40	< 0.001	59.9 ± 17.1	0.34	< 0.001
Bones	yes	105	29.7 ± 7.5			66.1 ± 16.1		
	no	1092	25.9 ± 7.8	0.50	< 0.001	59.9 ± 17.1	0.37	< 0.001
Heart	yes	95	28.4 ± 8.0			64.6 ± 16.1		
	no	1102	26.1 ± 7.8	0.29	< 0.01	60.1 ± 17.2	0.27	< 0.05
Kidneys	yes	60	28.5 ± 7.3			64.5 ± 16.1		
	no	1037	26.1 ± 7.9	0.32	< 0.05	60.3 ± 17.2	0.25	n.s.
Other	yes	191	28.4 ± 7.1			64.4 ± 15.4		
	no	1006	25.8 ± 7.9	0.35	< 0.001	59.7 ± 17.4	0.28	0.001
Number of organs	< 3	813	25.3 ± 7.7			58.8 ± 17.2		
	≥ 3	384	28.3 ± 7.8	0.39	< 0.001	64.1 ± 16.6	0.31	< 0.001

d: Cohen's effect size, FAS: Fatigue Assessment Scale; MFI: Multidimensional Fatigue Inventory, M: mean, SD: standard deviation. N: number of cases, n.s.: not significant, p: level of statistical significance

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Table 3. The association of medication and fatigue

			FAS			MFI		
Medication		N	M ± SD	d	p	M ± SD	d	p
Prednisolone	yes	542	27.1 ± 7.8			62.8 ± 17,1		
	no	655	25.5 ± 7.9	0.20	< 0.001	58.5 ±17.0	0.25	< 0.001
Azathioprine	yes	60	27.5 ± 8.1			62.3 ± 16.4		
	no	1137	26.2 ± 7.9	0.16	n. s.	60.4 ± 17.2	0.11	n. s.
Methotrexate	yes	34	29.9 ± 9.3			67.4 ± 17.0		
	no	1163	26.1 ± 7.8	0.44	< 0.01	60.3 ± 17.2	0.42	< 0.05
Number of Medications	≤ 1	1120	26.1 ±7.8			60.3± 17.2		
	> 1	77	28.2 ± 8.5	0.26	< 0.05	63.6± 16.5	0.19	n.s.

d: Cohen's effect size, FAS: Fatigue Assessment Scale; MFI: Multidimensional Fatigue Inventory, M: mean, N: number of cases, n.s.: not significant p: level of statistical significance, SD: standard deviation, y.: years.

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Table 4. The association of comorbidity and fatigue

		FAS				MFI		
Comorbidity		N	M ± SD	d	p	M ± SD	d	p
Arterial hypertension	yes	452	27.1 ± 8.0			63.4 ± 16.8		
	no	738	25.7 ± 7.7	0.19	< 0.01	58.6 ± 17.3	0.28	< 0.001
Disease of thyroid gland	yes	320	26.8 ± 8.1			61.9 ± 16.4		
	no	869	26.0 ± 7.9	0.11	n.s.	59.5 ± 17.2	0.10	n.s.
Obesity (BMI ≥30)	yes	320	28.3 ± 8.0			65.5 ± 16.3		
	no	875	25.5 ± 7.7	0.35	< 0.001	58.7 ± 17.2	0.41	< 0.001
Restless legs syndrome	yes	186	28.8 ± 7.7			65.9 ± 16.5		
	no	998	25.8 ± 7.9	0.38	< 0.001	59.5 ± 17.2	0.38	< 0.001
Diabetes mellitus	yes	134	27.7 ± 8.0			66.3 ± 16.0		
	no	1060	26.1 ± 7.8	0.21	< 0.05	59.7 ± 17.2	0.39	< 0.001
Sleep apnoea	yes	104	31.0 ± 7.8			70.1 ± 14.6		
	no	1084	25.8 ± 7.8	0.68	< 0.001	59.5 ± 17.2	0.67	< 0.001
Pulmonary hypertension	yes	38	30.2 ± 8.1			72.6 ± 13.5		
	no	1138	26.1 ± 7.8	0.52	< 0.001	59.9 ± 17.2	0.83	< 0.001
Number of concomitant diseases	< 3	1002	25.7 ± 7.7			58.9 ± 17.1		
	≥ 3	195	29.2 ± 7.9	0.45	< 0.001	68.2 ± 15.4	0.57	< 0.001

d: Cohen's effect size, FAS: Fatigue Assessment Scale; MFI: Multidimensional Fatigue Inventory, M: mean, N: number of cases, p: level of statistical significance, SD: standard deviation.

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Table 5. Demographic and medical factors as predictors of fatigue

	B	SE (B)	Beta	T	p
FAS (mult. R: 0.28)					
Affected organs (sum)	0.69	0.165	0.122	4.18	< 0.001
Comorbidity (sum)	1.41	0.229	0.186	6.14	< 0.001
Medication (sum)	1.09	0.345	0.092	3.17	< 0.01
Age	-0.09	0.020	-0.128	-4.31	< 0.001
Sex (female)	1.09	0.475	0.066	2.29	< 0.05
MFI (mult. R: 0.29)					
Affected organs (sum)	1.20	0.361	0.097	3.32	< 0.001
Comorbidity (sum)	3.47	0.501	0.210	6.93	< 0.001
Medication (sum)	2.85	0.754	0.109	3.78	< 0.001
Age	-0.06	0.045	-0.043	-1.45	n.s.
Sex (female)	2.59	1.040	0.071	2.50	< 0.05

B: Regression Coefficient, Beta: Partial Regression Coefficient FAS: Fatigue Assessment Scale, MFI: Multidimensional Fatigue Inventory, mult. R: multiple Regression coefficient, p: level of significance, SE (B): Standard Error of B, T: T-value