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Association between physical functions and quality of life in sarcoidosis

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Abstract. *Background:* Quality of life (QOL) is often reduced in patients with sarcoidosis. Studies of the associations between physical functions and QOL are lacking. *Objectives:* So the aims of this study were (i) to evaluate the associations between QOL and physical functions, including muscle strength and exercise capacity, and other clinical characteristics, and (ii) to evaluate whether these associations change over a two-year period. *Methods:* Eighty-eight sarcoidosis patients (61 men; mean age: 46.1 ± 10.2 years) participated in a two-year follow-up to cross-sectional study. All patients completed the short World Health Organization Quality of Life assessment instrument (WHOQOL-BREF) and Fatigue Assessment Scale (FAS) at the baseline and follow-up assessments. Patients also performed a six-minute walk test (6MWT) and elbow flexor muscle strength, quadriceps and hamstrings peak torque tests. Maximal inspiratory pressure was recorded. *Results:* QOL in sarcoidosis remained stable over a two-year course of the disease, and was reduced compared with healthy controls, particularly regarding the physical health domain. Fatigue and the six-minute walking distance showed strong associations with QOL at both baseline and follow-up. Fatigue and exercise capacity predicted the scores for the WHOQOL-BREF physical health domain at baseline (59%) and follow-up (64%). QOL at baseline was the best predictor of QOL at follow-up. *Conclusions:* QOL is reduced in sarcoidosis. Fatigue and exercise capacity showed important stable associations with QOL, especially in the physical health domain. FAS and 6MWT should therefore be included in the management of sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 117-128)*

Key words: Quality of life; Exercise capacity; Muscle strength; Fatigue; Sarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown origin. The course and impact of the disease are variable, depending on the organs involved and the intensity of the inflammation. Although virtually every organ can be involved, the lungs, lymphatic system, skin and eyes are frequently affected. Apart from organ-specific symptoms patients also have to deal with side-effects of medical treatments and non-specific health complaints, such as fatigue and physical impairments (1-4). These sarcoidosis-related disabling symptoms can significantly reduce a person's quality of life (QOL), especially in chronic sarcoidosis (5-7).

Health care professionals mostly rely on improvements of clinical parameters to determine

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treatment outcomes in sarcoidosis, and give less attention to subjective feelings of well-being, such as QOL (1,2). Nowadays, however, QOL is regarded as an important aspect of disease management in general (8). QOL refers to patients' perception or evaluation of their overall functioning in daily life. In other words, it reflects how satisfied patients are about their functioning in daily life (9). QOL measurements are essential in patient-centered care to identify patients' needs, and should be one of the major therapeutic outcome measures used to individualize the management of sarcoidosis. Since QOL is an abstraction, a key to improving it is understanding the association between QOL and functional impairments. For instance, physical impairments and fatigue complaints due to sarcoidosis can induce patients to reduce their daily activities, resulting in general deconditioning and possibly a reduced QOL. For these patients, exercise training might be considered as an adjunct therapy to improve QOL indirectly by improving exercise capacity and muscle strength. Thus, knowledge about aspects that influence QOL in sarcoidosis is of great clinical relevance (10,11).

Clinical parameters, such as lung function test results and chest radiographs, correlate only weakly with QOL (5,7,12,13). Moreover, it is well-known that fatigue, one of the major problems in sarcoidosis, substantially affects QOL (6,12,13). Recently, Marcellis et al. reported muscle weakness and exercise intolerance to be frequent problems in sarcoidosis (3). Nevertheless, studies about the influence of physical functions on QOL are lacking, as most studies have assessed the relationship between physical functions and health status instead of QOL (11,14-17). Health status, which is often reduced in sarcoidosis, refers to the impact of health-related factors, such as disease (for example sarcoidosis) and its treatment, on patients' functioning. Using health status measures to assess QOL can thus be misleading (9,11,18,19). A few studies found that peripheral muscle strength (11) and inspiratory muscle endurance (16,17) correlated with health status in sarcoidosis. However, the study populations were rather small (11,16,17) or only included sarcoidosis patients with specific health complaints (11). And the associations between physical impairments and health status were calculated using bivariate correlations rather than multiple regression analyses, so without correction for the influence of possible confounding variables. Exercise capacity has also proved to be associated with health status (14,15).

The aims of this study were therefore to evaluate the associations between QOL and physical functions, including muscle strength and exercise capacity, and other clinical characteristics, and to evaluate whether these associations change over a two-year period.

Methods

Subjects

Between November 2008 and September 2009, 124 symptomatic sarcoidosis patients referred to the interstitial lung disease (ild) care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC; Maastricht, the Netherlands) were included in a cross-sectional study (20). Patients were diagnosed based on consistent clinical features and bronchoalveolar lavage fluid analysis and/or biopsy-proven noncaseating epithelioid cell granulomas, according to the WASOG (World Association of Sarcoidosis and Other Granulomatous Disorders) guidelines (1). Between July 2010 and September 2011, all participants of the 2008/9 study (20) living in the southern part of the Netherlands (n=104) were invited to participate in a follow-up measurement.

Measurements

All measurements in this study have been described previously (20). The QOL and fatigue scores and the physical test results of the 2008/9 cross-sectional study were used as baseline values (20). During the 2008/9 study, a healthy control group (n = 62) matched for age and sex was recruited from hospital employees and the surrounding community (Table 1; (20)). These data were used as reference values for QOL scores, fatigue scores and physical test results for both the baseline and follow-up measurements.

This study was approved by the local Medical Ethics Committee of the MUMC (MEC 09-4-007). Written informed consent was obtained from all participants.

Table 1. Summary of the demographic, clinical and physical characteristics of the sarcoidosis patients studied at baseline and follow-up and the healthy controls.

	Sarcoidosis patients at baseline	Sarcoidosis patients at follow-up	Healthy controls
Demographics			
Subjects, n	88		62
Women/men, n	27/61		22/40
Age, yrs	46.1 ± 10.2		46.4 ± 9.9
Time since diagnosis, yrs	5.9 ± 5.8		NA
BMI, kg/m^2	28.4 ± 4.6	28.3 ± 4.6	24.7 ± 1.8
Nonsmokers/smokers, n	81/7	81/7	56/6
Medication			
Prednisone use yes/no, n	35/53	31/57	0/62
Prednisone dosage, mg	12.5 ± 6.9	7.5 ± 3.2*	0
Methotrexate use yes/no, n	29/59	33/55	0/62
Methotrexate dosage, mg	10.8 ± 2.8	10.0 ± 3.5	0
Anti-TNF-α use yes/no, n	14/74	22/66*	0/62
Lung function tests			
DLCO, % pred	76.4 ± 17.4	77.0 ± 18.0	NA
FVC, % pred	98.2 ± 19.5	98.9 ± 18.0	NA
FEV_1, % pred	84.1 ± 21.3	85.1 ± 22.0	NA
Chest radiograph stages			
0+I / II+III / IV, n	34/33/21	34/33/21	NA
Inflammatory markers			
CRP[#]	8.1 ± 12.7	3.8 ± 3.7*	NA
sIL-2R[¶]	2995 ± 1501	2366 ± 1505*	NA
Fatigue measure			
FAS score	28.6 ± 7.2	26.6 ± 7.1*	15.6 ± 4.0
Physical functions (women/men)			
6MWD, m	551 ± 88 / 606 ± 90	572 ± 86 / 625 ± 97*	679 ± 73 / 747 ± 74
6MWD, % pred	81.2 ± 13.0 / 81.0 ± 12.1	84.2 ± 12.7 / 83.7 ± 13.0*	NA
EFMS, N	158.9 ± 26.9 / 258.1 ± 55.0	159.0 ± 29.1 / 247.4 ± 67.5	162.6 ± 22.9 / 287.0 ± 47.9
EFMS, % pred	97.7 ± 16.6 / 89.9 ± 19.2	97.8 ± 17.9 / 86.2 ± 23.5	NA
QPT180, Nm	59.6 ± 20.1 / 96.4 ± 30.7	64.8 ± 19.6* / 98.9 ± 31.3	70.2 ± 13.3 / 118.4 ± 23.0
QPT180, % pred	84.9 ± 28.7 / 81.4 ± 25.9	92.3 ± 27.9* / 83.5 ± 26.4	NA
HPT180, Nm	47.8 ± 16.3 / 70.7 ± 23.4	47.5 ± 12.1 / 72.0 ± 23.2	55.3 ± 15.3 / 86.3 ± 18.7
HPT180, % pred	86.4 ± 29.5 / 81.9 ± 27.2	85.9 ± 21.8 / 83.4 ± 26.9	NA
PImax, % pred	87.1 ± 33.4 / 79.3 ± 25.8	85.2 ± 28.8 / 83.3 ± 24.4	NA

Data are expressed as mean ± standard deviation (SD) or absolute numbers (n).
*Sarcoidosis patients (n=88) at baseline versus follow-up: *p<0.05.*
Abbreviations: BMI = body mass index; TNF = tumor necrosis factor; DLCO = diffusing capacity of the lung for carbon monoxide; % pred = % of predicted value; FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; CRP = C-reactive protein; sIL-2R = soluble interleukin-2 receptor; FAS = Fatigue Assessment Scale; 6MWD = six-minute walking distance; EFMS = elbow flexor muscle strength; QPT180 and HPT180 = isokinetic quadriceps and hamstrings peak torques at 180° per second; PImax = maximal inspiratory pressure; NA = not applicable
[#]: normal range <10 mg/L; [¶]: normal range 240-3,154 pg/ml

Clinical data

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured with a pneumotachograph (Masterlab, Jaeger, Würzburg, Germany). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured using the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as percentage of the predicted value (21).

The C-reactive protein (CRP) concentration was measured by a turbidimetric method on the SYNCHRON LX® (Beckman Coulter Inc., Fullerton, CA, USA). The normal value for CRP is <10 $mg.L^{-1}$. The serum levels of soluble interleukin-2 receptor (sIL-2R) were analyzed using commercially available Diaclone ELISA kits (Sanquin, Amsterdam, the Netherlands). Normal values are between 240 and 3,154 $pg.mL^{-1}$ (22).

Questionnaires

The World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF), an abbreviated version of the WHOQOL-100, is a generic, cross-culturally developed comprehensive measure of QOL. It consists of 24 questions in four domains (physical health, psychological health, social relationships and environment) related to QOL and two questions that assess the facet of overall QOL and general health. Each question uses a 5-point Likert scale. The psychometric properties of the WHOQOL-BREF have been found to be good, including for sarcoidosis patients (23-25).

Fatigue was measured with the 10-item Fatigue Assessment Scale (FAS). Each item uses a 5-point rating scale, so FAS scores range from 10 to 50. FAS scores below 22 indicate nonfatigued persons, scores of 22-34 indicate fatigued persons, and scores of 35 or more indicate extremely fatigued persons. The psychometric properties of the FAS in sarcoidosis patients are good (26).

Exercise capacity and muscle strength

The Six-Minute Walk Test (6MWT) was used to assess exercise capacity, and was performed according to the American Thoracic Society guidelines (27).

The Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, New York, USA) was used to measure isokinetic peak torques (in Nm) of the hamstrings and quadriceps of the dominant leg, with a velocity of 180°/s as described previously (28). The Biodex is a reliable and valid isokinetic dynamometer (29,30).

Maximal isometric strength (in Newton) of the elbow flexors was measured with the microFET (Biometrics, Almere, the Netherlands) (31). This hand-held dynamometer is a reliable measurement instrument (31,32).

Maximal inspiratory pressure (PImax) was assessed by measuring maximal respiratory mouth pressures (33). Data from the study by Harik-Khan et al. (n= 267 healthy subjects) were used as reference values (34).

Statistical analysis

Demographic, clinical, and physical data are expressed as mean ± standard deviation (SD) and, where appropriate, in absolute numbers. Paired sample t-tests were used to test mean differences in continuous data of the patient group between baseline and follow-up, while nominal data were analyzed using McNemar's test. To detect statistically significant differences between the patient and control groups, continuous data were analyzed with independent sample t-tests, while nominal data were tested using Chi-square tests (35).

Associations between the domains of the WHOQOL-BREF and the continuous demographic, clinical, and physical characteristics of the patient group were calculated using Pearson's correlations. Differences in WHOQOL-BREF domain scores in relation to sex, prednisone and methotrexate use, and radiographic stages were explored by means of independent sample t-tests and one-way ANOVA. Variables with a significant association (p-value <0.05) with the domains of the WHOQOL-BREF were selected for the multiple regression analysis (backward method). Multiple regression analyses were used to assess the association between QOL and both clinical and physical parameters and also to assess the predictive value of these parameters at baseline for the QOL measured at follow-up. P-values <0.05 were considered statistically significant.

All analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Table 2. Summary of the quality of life characteristics, measured with the WHOQOL-BREF, of the sarcoidosis patients studied at baseline (t0) and follow-up (t1) and the healthy controls.

	Sarcoidosis patients t0	Sarcoidosis patients t1	Controls (n= 62)	Mean difference sarcoidosis t1 vs t0 (95%CI)	Mean difference controls vs sarcoidosis t0 (95%CI)	Mean difference controls vs sarcoidosis t1 (95%CI)
WHOQOL-BREF						
Overall QOL facet	5.9 ± 1.5	6.3 ± 1.6	8.7 ± 1.0	0.4 (0.2 to 0.7)*	2.9 (2.5 to 3.3)#	2.4 (2.0 to 2.8)#
Physical Health	12.4 ± 2.8	13.3 ± 2.8	17.9 ± 1.5	0.8 (0.4 to 1.3)*	5.5 (4.8 to 6.2)#	4.7 (4.0 to 5.4)#
Psychological Health	13.8 ± 2.4	14.3 ± 2.4	17.0 ± 1.9	0.5 (0.1 to 0.9)*	3.2 (2.5 to 3.9)#	2.7 (2.0 to 3.4)#
Social Relationships	15.2 ± 3.1	15.4 ± 2.5	17.3 ± 2.4	0.3 (-0.2 to 0.8)	2.2 (1.2 to 3.1)#	1.9 (1.1 to 2.7)#
Environment	15.8 ± 2.4	15.8 ± 2.1	18.0 ± 1.6	0.0 (-0.4 to 0.4)	2.2 (1.6 to 2.9)#	2.2 (1.6 to 2.8)#

Data are expressed as mean ± standard deviation (SD).
Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life-BREF assessment instrument; QOL = quality of life
** p<0.05; # p<0.001*

Results

Patient characteristics

In total, 104 participants of the 2008/9 study were invited to participate in the follow-up study. Fourteen of these patients were unable to participate for the following reasons: death (n=2), exacerbations of sarcoidosis (n=2), health problems other than sarcoidosis (n=4), and change of address without notice (n=6). Two patients did not complete the WHOQOL-BREF, the primary outcome measure of this study. In the end, 88 patients (mean follow-up 1.9 ± 0.4 years) participated. The demographic, clinical, and physical data of the patients at baseline and follow-up are summarized in table 1. During the two years of follow-up, more patients had started to use methotrexate and anti-TNF-α medication, resulting in a reduced prednisone usage.

Since no differences in demographic, clinical, or physical characteristics were found between the patients who dropped out and those remaining in the study, those participating in the follow-up study were regarded as a representative sample of the patients studied in 2008/9 (3).

The sarcoidosis patients showed significantly lower mean scores on the general evaluative facet and all domains of the WHOQOL-BREF compared with healthy controls, both at baseline and follow-up. The largest difference between the patient group and healthy controls emerged for the physical health domain (table 2). The sarcoidosis group showed no differences in mean scores between the baseline and follow-up measurements for the social relationships and environment domains. Although the changes in mean scores on the general evaluative facet and the physical and psychological health domains between baseline and follow-up measurements were very small, the scores showed a statistically significant improvement at the follow-up measurement compared with the baseline measurement (Fig. 1).

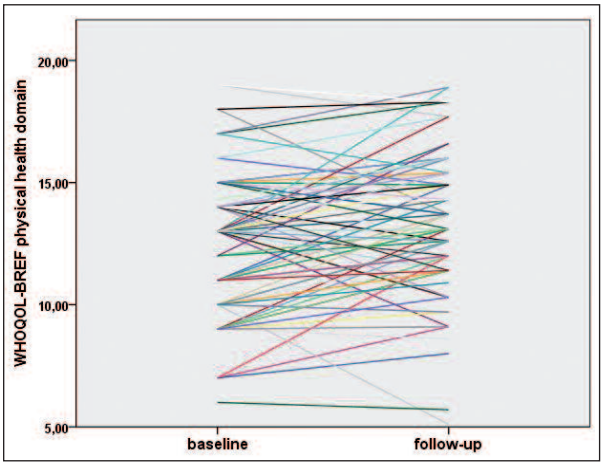

Fig. 1. Individual changes in WHOQOL-BREF scores, physical health domain, of the sarcoidosis patients studied.

Table 3. Correlations between the physical and clinical characteristics of the sarcoidosis patients studied and their WHOQOL-BREF scores.

	WHOQOL-BREF				
	Overall QOL facet	Physical health	Psychological health	Social relationships	Environment
Baseline					
FAS score	-0.45#	-0.74#	-0.60#	-0.28*	-0.40#
6MWD, % pred	0.27*	0.34*			0.33*
EFMS, % pred	0.23*	0.31*			
HPT180, % pred	0.23*	0.25*			0.23*
PImax					0.28*
DLCO, % pred					0.25*
Follow-up					
FAS score	-0.67#	-0.76#	-0.75#	-0.40#	-0.56#
6MWD, % pred	0.39#	0.43#	0.29*	0.26*	0.38#
EFMS, % pred	0.24*	0.25*			
HPT180, % pred	0.31*	0.26*		0.23*	
QPT180, % pred	0.25*			0.23*	
PImax				0.28*	
DLCO, % pred		0.28*			

*Data are expressed as Pearson correlation. Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life-BREF assessment instrument; FAS = Fatigue Assessment Scale; 6MWD = six-minute walking distance; % pred = % of predicted value; EFMS = elbow flexor muscle strength; HPT180 and QPT180 = isokinetic hamstrings and quadriceps peak torques at 180° per second; PImax = maximal inspiratory pressure; DLCO = diffusing capacity of the lung for carbon monoxide. *p<0.05; #p<0.001*

Associations with quality of life

In general, the FAS scores at baseline showed medium to high correlations with all domains of the WHOQOL-BREF (table 3). The FAS score showed the best correlation with the physical health domain. Besides the FAS scores, the following clinical and physical variables were included in the multiple regression analyses for the overall QOL facet (six-minute walking distances (6MWDs), elbow flexor muscle strength (EFMS) and hamstrings peak torque (HPT)) and the physical health (6MWDs, EFMS, and HPT) and environment (DLCO, 6MWDs, HPT, and PImax) domains of the WHOQOL-BREF. Multiple regression analyses demonstrated that fatigue had strong associations with all domains of the WHOQOL-BREF at baseline, while the 6MWD was strongly associated with the overall QOL facet and the physical health and environment domains, predicting 8 to 59% (table 4).

At the follow-up measurement, the FAS scores showed moderate to high and the 6MWDs low to moderate correlations with all domains of the WHOQOL-BREF (table 3). The following variables were also included in the multiple regression analyses for the overall QOL facet (EFMS, quadriceps peak torque (QPT), HPT, and prednisone use) and the physical health (DLCO, EFMS, and HPT) and social relationships (QPT, HPT, PImax, and prednisone use) domains of the WHOQOL-BREF. The multiple regression analyses at follow-up also showed that fatigue had strong associations with all domains of the WHOQOL-BREF, while the 6MWD was strongly associated with the overall QOL facet and the physical health and environment domains, predicting 34 to 64% (table 4).

Both at baseline and follow-up, the physical health domain was best predicted by FAS scores and 6MWDs (59% and 64%, respectively; table 4). The correlations between FAS scores and 6MWDs were

Table 4. Clinical and physical predictors of the WHOQOL-BREF measured at baseline and follow-up.

	WHOQOL-BREF				
	Overall QOL facet	Physical health	Psychological health	Social relationships	Environment
	B (SE B) β	B (SE B) β	B (SE B) β	B (SE B) β	B (SE B) β
Baseline					
Constant	6.45 (1.23) -	16.39 (1.68) -	19.48 (0.84) -	18.54 (1.32) -	14.92 (2.13) -
FAS score	-0.08 (0.02) -0.41#	-0.27 (0.03) -0.70#	-0.20 (0.03) -0.60#	-0.12 (0.05) -0.28*	-0.11 (0.04) -0.32*
6MWD, % pred	0.02 (0.01) 0.18	0.05 (0.02) 0.20*			0.05 (0.02) 0.25*
R^2	0.23	0.59	0.36	0.08	0.20
Follow-up					
Constant	7.72 (1.10) -	16.39 (1.76) -	21.06 (0.67) -	20.03 (0.85) -	16.38 (1.65) -
FAS score	-0.13 (0.18) -0.60#	-0.28 (0.03) -0.70#	-0.25 (0.03) -0.75#	-0.15 (0.03) -0.45#	-0.14 (0.03) -0.48#
6MWD, % pred	0.03 (0.01) 0.21*	0.05 (0.02) 0.23*			0.04 (0.02) 0.23*
Prednisone use				-1.55 (0.48) -0.31*	
R^2	0.47	0.64	0.56	0.34	0.35

Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life-BREF assessment instrument; QOL = quality of life; FAS = Fatigue Assessment Scale; 6MWD = six-minute walking distance; % pred = % of predicted value
**p<0.05; #p<0.001.*

weak, so there was no multicollinearity between these variables.

Predictive value of baseline variables for QOL measured at follow-up

Table 5 shows the correlations between the baseline physical and clinical characteristics and follow-up WHOQOL-BREF scores of the sarcoidosis patients. Multiple regression analyses showed that WHOQOL-BREF scores measured at baseline were the most predictive variables (β between 0.46 and 0.71; all p-values <0.001) for QOL at follow-up (table 6).

The predictive value of the clinical and physical variables measured at baseline for QOL at follow-up was also analyzed. To this end, the baseline WHOQOL-BREF scores were excluded from the multiple regression analyses. The results of these analyses were similar to those mentioned under the previous heading. Fatigue measured at baseline (β between -0.29 and -0.41; all p-values <0.001) was an important negative predictor of the WHOQOL-BREF domains, followed by the 6MWD (β between 0.23 and 0.27; all p-values <0.05), predicting 10 to 27% (table 6).

Discussion

The aims of this study were to evaluate the associations between QOL, measured with the WHOQOL-BREF, and physical functions, including muscle strength and exercise capacity, and other clinical characteristics (fatigue, lung function test results, radiographic stages, medication use and inflammatory markers), and to evaluate whether these associations changed over a two-year course of the disease. In agreement with previous studies (5,7), the present study found reduced QOL in patients with sarcoidosis compared with healthy controls. The main outcomes of this study were that fatigue and 6MWD were associated with QOL. In particular, the most affected domain, that of physical health, showed strong associations with fatigue and exercise capacity at baseline and follow-up. These associations remained stable during the two-year course of sarcoidosis we investigated. When QOL at baseline was taken into account, these scores best predicted QOL at follow-up.

QOL is currently a major topic in the management of chronic diseases. QOL refers to patients' perception or evaluation of their overall functioning

Table 5. Correlations between baseline physical and clinical characteristics of the sarcoidosis patients studied and their follow-up WHOQOL-BREF scores.

WHOQOL-BREF					
			Follow-up		
	Overall QOL facet	Physical health	Psychological health	Social relationships	Environment
Baseline					
FAS score	-0.34*	-0.44#	-0.46#	-0.23*	-0.35*
6MWD, % pred	0.32*	0.34*	0.32*	0.22*	0.31*
EFMS, % pred	0.27*	0.28*			
QPT180, % pred	0.25*			0.23*	
HPT180, % pred	0.29*	0.23*	0.22*	0.25*	
DLCO, % pred		0.22*			
WHOQOL-BREF					
Overall QOL facet	0.65#	0.49#	0.54#	0.34*	0.36*
Physical health	0.57#	0.71#	0.51#	0.37#	0.49#
Psychological health	0.47#	0.37#	0.67#	0.41#	0.46#
Social relationships	0.28*	0.24*	0.41#	0.69#	0.43#
Environment	0.48#	0.47#	0.42#	0.47#	0.69#

Data are expressed as Pearson correlation.
Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life-BREF assessment instrument; QOL = quality of life; FAS = Fatigue Assessment Scale; 6MWD = six-minute walking distance; % pred = % of predicted value; EFMS = elbow flexor muscle strength; QPT180 and HPT180 = isokinetic hamstrings and quadriceps peak torques at 180° per second; DLCO = diffusing capacity of the lung for carbon monoxide
**p<0.05; #p<0.001*

in daily life (9). Using QOL measures as intervention outcome measures is useful to determine the treatment benefits for patients (8). The World Health Organization Quality of Life-100 and BREF questionnaires are both good instruments to assess QOL in sarcoidosis (23-25). In line with previous studies, we found a reduced QOL in patients with sarcoidosis compared with healthy controls, especially in the physical health domain (5). This implies that patients felt physically less healthy than the healthy controls. In line with the results of the present study, Alilovic et al. (7) also found reduced QOL in Croatian sarcoidosis patients, measured with the WHOQOL-BREF, in the domains of physical and psychological health, in comparison to healthy controls. In contrast to our study, Alilovic et al. (7) found that sarcoidosis patients reported a better perceived QOL than healthy controls as regards the domains of social relationships and environment. Although the WHOQOL-BREF scores of the patients in the present study were largely similar to theirs, the scores of our healthy controls were higher.

In agreement with Michielsen et al., the present study found that fatigue is an important negative predictor of QOL (12,13). Fatigue is a clear hallmark of sarcoidosis, with a prevalence of 60-90% (3,36,37). The subjective FAS appeared to be a good measure to assess and evaluate fatigue complaints. The FAS is easy to complete and not time-consuming (1-2 minutes). The digital version can be completed at home or even during a visit to the patient's own physician (www.ildcare.nl/pages/artsen_informatie_fasnl.html) (6,38-40).

Several studies have reported that exercise intolerance and muscle weakness are frequent problems in sarcoidosis patients, and these impairments show a stable and persistent character (3,11,20,41). The present study found a positive association between QOL, particularly in the physical health domain, and exercise capacity measured with the 6MWT. Michielsen et al. (13) did not report exer-

Table 6. Predictive value of clinical and physical variables measured at baseline and follow-up for the WHOQOL-BREF scores measured at follow-up.

	WHOQOL-BREF measured at follow-up				
	Overall QOL facet	Physical health	Psychological health	Social relationships	Environment
	B (SE B)	B (SE B)	B (SE B)	B (SE B)	B (SE B)
Baseline variables (WHOQOL-BREF included)					
Constant	0.86 (0.67) -	4.21 (1.01) -	2.19 (1.50) -	5.87 (1.10) -	6.22 (1.08) -
WHOQOL-BREF					
Overall QOL facet	0.48 (0.11) 0.46#				
Physical health	0.15 (0.06) 0.27*	0.73 (0.08) 0.71#	0.15 (0.08) 0.17		
Psychological health			0.56 (0.09) 0.56#		
Social relationships				0.55 (0.06) 0.68#	
Environment					0.61 (0.07) 0.69#
QPT180, % pred	0.01 (0.01) 0.14			0.02 (0.01) 0.16*	
6MWD, % pred			0.03 (0.02) 0.15		
R^2	0.49	0.51	0.51	0.50	0.48
Baseline variables (WHOQOL-BREF not included)					
Constant	5.33 (1.34) -	13.10 (2.36) -	14.54 (1.98) -	15.66 (1.48) -	14.81 (1.78) -
FAS score	-0.06 (0.02) -0.29*	-0.16 (0.04) -0.40#	-0.14 (0.03) -0.41#	-0.06 (0.04) -0.19	-0.09 (0.03) -0.29*
6MWD, % pred	0.03 (0.01) 0.27*	0.06 (0.02) 0.25*	0.05 (0.02) 0.23*		0.04 (0.02) 0.25*
HPT180, % pred				0.02 (0.01) 0.21*	
R^2	0.19	0.27	0.26	0.10	0.18

Abbreviations: WHOQOL-BREF = World Health Organization Quality of Life-BREF assessment instrument; QOL = quality of life; QPT180 and HPT180 = isokinetic quadriceps and hamstrings peak torques at 180º per second; % pred = % of predicted value; 6MWD = six-minute walking distance; FAS = Fatigue Assessment Scale
**p<0.05; #p<0.001*

cise capacity to be a predictor of QOL. However, their study measured exercise capacity with a symptom inventory questionnaire. Bourbonnais et al. (15) and Baughman et al. (14) reported positive relationships between 6MWD and health status measures such as the Sarcoidosis Health Questionnaire (SHQ), 36-item Short-Form Health Survey (SF-36) and St. George's Respiratory Questionnaire (SGRQ).

The present study found no associations between QOL and either inspiratory or peripheral muscle strength. These results are in line with those reported by Wirnsberger et al. (16). However, in a study by Wirnsberger et al., (16) respiratory muscle endurance time did correlate with the Sickness Impact Profile (SIP) subscales for "mobility" and "body care and movement". Brancaleone et al. (17) found correlations between inspiratory muscle endurance and SF-36 scores, especially the physical subscales. Spruit et al. (11) also found positive correlations between quadriceps strength and SF-36 scores.

QOL measured at baseline appeared to be the best predictor of QOL measured at follow-up in our study. After the WHOQOL-BREF scores measured at baseline were excluded from the multiple regression analyses, fatigue and exercise capacity appeared to be good predictors of QOL at follow-up. These results are not surprising, since group mean WHOQOL-BREF scores did not show relevant changes between baseline and follow-up (Fig. 1).

In patient-centered care/personalized medicine, in which the patient has a central role, physicians should be more aware of the impact of sarcoidosis on their patients' subjective feelings of well-being and

needs. In the management of sarcoidosis, physicians should not only focus on objective, but also on subjective clinical parameters, including QOL. Since QOL is an abstraction, a key to improving it is understanding the association between QOL and functional impairments. For instance, physical therapists try to influence a patient's functions and activities, which in turn might improve QOL. Commonly used clinical parameters, such as lung function test results or chest radiographs, have been found to be not or only weakly associated with QOL (5,7,12). Studies about the impact of physical functions on QOL are lacking, since most studies have measured health status instead of QOL. Health status refers to the impact of health-related factors, such as disease (for example sarcoidosis) and its treatment, on patients' functioning. Generally used health status measures are the SF-36, SHQ, SIP, SGRQ and King's Sarcoidosis Questionnaire (KSQ) (9,42). Since QOL and health status are two different concepts with different levels of differentiation, one may wonder whether it is possible for patients to differentiate between these concepts.

To our best knowledge, ours is the first longitudinal study in sarcoidosis to examine associations between QOL and physical functions. We found that the associations between QOL and both fatigue and exercise capacity remained stable over the two-year course of the disease we investigated. These results suggest that fatigue complaints and exercise intolerance have a significant impact on daily living and QOL. These impairments may therefore be important intervention targets to indirectly improve the QOL of patients with sarcoidosis. The present study found no multicollinearity between FAS scores and 6MWDs. Braam et al. (43) also found that fatigue in sarcoidosis cannot be objectified by repeated exercise testing. Previous studies also concluded that both fatigue measures and exercise tests should be included in the management of sarcoidosis (20). Alilovic et al. (7) stated that a fatigue measure should be used in addition to the WHOQOL-BREF to improve the QOL evaluation.

Successful treatment of sarcoidosis frequently fails to eradicate the symptoms of sarcoidosis-associated fatigue. Pharmacologic strategies for fatigue mostly focus on the use of neurostimulants, neurostimulant-like drugs and tumor necrosis factor-α inhibitors (38). Heij et al. (44) showed that ARA290 reduced symptoms related to small fiber neuropathy in sarcoidosis, including fatigue. They also reported an improvement in the physical functioning dimensions of the SF-36 health status questionnaire.

Physical deconditioning may also be a cause of fatigue and exercise intolerance reducing QOL. Fatigue and physical impairments may induce patients to reduce their daily physical activities, resulting in general deconditioning. This in turn will increase the degree of fatigue and exercise intolerance, causing a further reduction of daily activities (negative vicious circle of physical deconditioning) (11,45). Exercise training could therefore be considered for patients with physical impairments and/or fatigue complaints. Several studies have reported that exercise training in chronic diseases was effective in treating physical impairments and improving QOL (46-48). Unfortunately, the effects of exercise training have never been studied in a representative sarcoidosis population.

Study limitations

This study included refractory sarcoidosis patients referred to a tertiary clinic as they suffered from severe physical complaints, which may have caused selection bias. This selection may have resulted in an overestimation of the QOL reduction.

The physical tests performed in this study are volitional tests, and the results partially depend on the patient's motivation and cooperation. Nonvolitional testing would possibly yield more valid results. However, the tests we used are generally accepted in clinical studies, (11) and in our experience, sarcoidosis patients are very cooperative and motivated to participate in research projects.

Future research

Since fatigue and exercise intolerance appeared to be important parameters affecting QOL, especially in the physical health domain, a prospective intervention study focusing on the clinical benefit of exercise training in the management of sarcoidosis is warranted.

Although the differences in QOL between baseline and follow-up measurements were statistically significant, they may be clinically irrelevant from the patients' point of view. However, the mini-

mal clinically important difference and the measurement error of the WHOQOL-BREF have not yet been studied.

We conclude that QOL is reduced in sarcoidosis. Fatigue and exercise capacity showed important associations with QOL, especially in the domain of physical health, and these associations remained stable over a two-year follow-up period. Hence, the FAS and 6MWT should be included in the management of sarcoidosis. Future studies should investigate whether exercise training might be useful.

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Author contributions

R.G.J.M. contributed to the design of the study and the collection and analysis of the data. He is also the main author of the manuscript. A.F.L. contributed to the design of the study and the collection and analysis of the data, and the writing and review of the manuscript. M.D. contributed to the design of the study and the collection and analysis of the data, and the writing and review of the manuscript. J.D.V. contributed to the analysis of the data and the writing and review of the manuscript. All authors had final responsibility for the decision to submit for publication and approved the version submitted.

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