Arthritis & Rheumatism
ARTHRITIS CARE & RESEARCH 47:8–16, 2002
DOI 10.1002/art1.10179

ORIGINAL ARTICLE

Assessment of Fatigue in Patients With Ankylosing Spondylitis: A Psychometric Analysis

ASTRID VAN TUBERGEN,[1] JOLANDA COENEN,[1] ROBERT LANDEWÉ,[1] ANNEKE SPOORENBERG,[1] ASTRID CHORUS,[2] ANNELIES BOONEN,[1] SJEF VAN DER LINDEN,[1] AND DÉSIRÉE VAN DER HEIJDE[3]

Objectives. **To investigate whether the single-item fatigue question of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Multidimensional Fatigue Inventory (MFI) are appropriate instruments to measure fatigue in ankylosing spondylitis (AS); to identify factors that influence fatigue in AS; and to assess how fatigue in all its aspects is associated with quality of life in AS.**

Methods. **A total of 812 patients with AS were included. Patients completed questionnaires on disease activity (BASDAI), functional ability (Bath Ankylosing Spondylitis Functional Index [BASFI]), global well-being (Bath Ankylosing Spondylitis Global Score [BAS-G]), overall perceived health (EuroQoL visual analog scale), and quality of life (Ankylosing Spondylitis Quality of Life questionnaire, and Short Form 36 [SF-36]). Patients were dichotomized into a F+ group (fatigue = major symptom) if the BASDAI fatigue score was > 5.0 and a F− group (fatigue = minor symptom) if the fatigue score was < 5.0. Reproducibility was assessed with intraclass correlation coefficients, and responsiveness was calculated according to 3 different methods. Logistic regression analysis was used to determine which factors were associated with fatigue. Multiple regression analysis was used to investigate whether fatigue contributes in explaining quality of life.**

Results. **Fifty-three percent of the patients were assigned to the F+ group. They scored significantly worse compared with the F− group with respect to each dimension of the MFI and to all other questionnaires studied (all $P < 0.001$). The BASDAI fatigue question, as well as each separate dimension of the MFI, showed moderate to good reproducibility (0.57–0.75) and responsiveness (0.23–0.96). Fatigue was, in the opinion of the patients, highly associated with pain (70% of patients) and stiffness (54% of patients). Logistic regression analysis showed that scores on BASDAI, BASFI, BAS-G, and mental health status (SF-36) were independently associated with fatigue ($R^2 = 0.52$). Multiple regression analysis showed that scores on the BASDAI fatigue question were significantly associated with quality of life. With the 5 MFI dimensions as explanatory variables, different aspects of fatigue were associated with different domains of quality of life.**

Conclusion. **Fatigue as a major symptom of AS can effectively be measured with either a single-item question on the intensity of fatigue or with the MFI. The MFI, however, provides more insight into specific dimensions of fatigue. Fatigue appears to be associated with the level of disease activity, functional ability, global well-being, and mental health status. In addition, fatigue negatively influences different aspects of quality of life.**

KEY WORDS. Fatigue; Ankylosing spondylitis; Questionnaires; Quality of life; Assessment.

INTRODUCTION

Fatigue has been acknowledged as an important symptom in ankylosing spondylitis (AS) (1–4). Although fatigue is a widely used term, no uniformly accepted definition is available. Belza described fatigue as "the enduring, subjective sensation of generalized tiredness or exhaustion" (5). Fatigue appears to be multifactorial and multidimensional: physiologic, psychological, social, and personal factors influence the presence and experience of fatigue (5–9).

During the Outcome Measures in Rheumatoid Arthritis Clinical Trials Conference in 1998—in followup of the Assessments in Ankylosing Spondylitis workshop in

[1]Astrid van Tubergen, MD, Jolanda Coenen, Robert Landewé, MD, PhD, Anneke Spoorenberg, MD, Annelies Boonen, MD, and Sjef van der Linden, MD, PhD: University Hospital Maastricht, Maastricht, The Netherlands; [2]Astrid Chorus, MSc: TNO Prevention and Health, Division of Public Health, Leiden, The Netherlands; [3]Désirée van der Heijde, MD, PhD: University Hospital Maastricht, Maastricht, The Netherlands, and Limburg University Center, Diepenbeek, Belgium.

Address correspondence to Astrid van Tubergen, MD, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: avantubergen@yahoo.com.

Submitted for publication February 20, 2001; accepted in revised form July 19, 2001.

Table 1. Patient populations used for various aspects of the study

		Spa therapy trial			
	SDR (n = 568)	**Arm 1 Spa therapy Austria (n = 40)**	**Arm 2 Spa therapy Netherlands (n = 40)**	**Arm 3 Controls (n = 40)**	**OASIS (n = 124)**
Comparison F+/F− scores questionnaires	X	X	X	X	X
Reproducibility fatigue questionnaires	—	—	—	X	—
Responsiveness fatigue questionnaires	—	X	—	X*	—
Factors influencing fatigue according to the patients	—	—	—	—	X
Factors implicitly influencing fatigue	X	—	—	—	X
Correlation fatigue with scores questionnaires	X	X	X	X	X
Influence fatigue on quality of life	X	—	—	—	X

X = Participating in this aspect of the study; SDR = Standardized Diagnosis Register of Rheumatic Diseases; OASIS = Observational Study on Outcome in Ankylosing Spondylitis.
* Only as control arm in the method according to Guyatt (1987).

1995—fatigue was considered to be an important domain in the core set for disease controlling antirheumatic therapy in AS, but a specific instrument to measure fatigue was not selected, because little information was available on assessing fatigue in AS (10). The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a widely used instrument to measure disease activity in patients with AS, and includes only 1 question concerning the degree of fatigue (2). Many questionnaires can be used for measuring fatigue multidimensionally, but none of them have been validated in AS (6,11–14). The Multidimensional Fatigue Inventory (MFI) is such a multidimensional questionnaire (12). The psychometric properties of the MFI have been validated and tested in several patient populations as well as in healthy subjects, but not yet in patients with AS (12,15–17).

The first aim of this study was to investigate whether the single-item BASDAI fatigue question and the MFI are appropriate instruments to measure fatigue in AS. Important aspects of outcome measures such as reproducibility and responsiveness will be investigated. After this first stage, both instruments were used to investigate the impact of fatigue in AS.

The second aim of this study was to assess which factors influence fatigue in AS. This was investigated by obtaining the opinion of patients with AS. We hypothesized that fatigue could be influenced by, among other factors, disease activity, sleep disturbance, weather, medication, and work. In addition, we wanted to identify factors, measured by AS-specific instruments, that are most strongly associated with fatigue.

A final aim was to assess how fatigue in all its aspects influences quality of life in patients with AS. To date, few data have been reported on the relationship between fatigue and quality of life in patients with AS (4).

PATIENTS AND METHODS

Patients. A total of 812 patients with AS were derived from 3 sources: 1) Five hundred sixty-eight patients from 15 Dutch outpatient departments of rheumatology, who completed a postal questionnaire. These centers participated in the Standardized Diagnosis Register (SDR), a nationwide diagnosis register of rheumatic diseases (18); patients from the Observational Study on Outcome in AS (OASIS) cohort study (see source 3 below) who also participated in this study were excluded, to avoid double counting. 2) One hundred twenty Dutch outpatients participating in a randomized controlled trial to assess the efficacy of a 3-week course of spa therapy in patients with AS (19). Patients were randomly allocated to receive either spa therapy in Austria (arm 1, n = 40), in The Netherlands (arm 2, n = 40), or to a control arm (n = 40) that stayed at home and continued standard treatment (antiinflammatory drugs and weekly group physical therapy). 3) One hundred twenty-four of 137 Dutch patients participating in OASIS. Table 1 shows the distribution of patients for the present study.

Questionnaires. The self-reports contained sociodemographic and disease-related questionnaires, specifically the MFI, BASDAI, Bath AS Functional Index (BASFI) (20), Bath AS Patient Global Score (BAS-G) (21), and Short Form-36 (SF-36) (22).

The MFI consists of 20 items covering 5 dimensions: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. Each dimension has 4 statements that are directed either positively or negatively. The answers are given on a 5-point scale (1 to 5), with the labels "yes, that is true," and "no, that is not true" at either end. Scores range from 4–20 on each dimension, with higher scores indicating greater fatigue. A summary score

of the 20 items is discouraged. If a single score on fatigue is required, the dimension "general fatigue" should be used (12).

The BASDAI, BASFI, and BAS-G are well-established instruments that are widely used in clinical trials and epidemiologic studies to evaluate disease activity, functioning, and global well-being in patients with AS. They have been shown to be valid, reliable, and discriminatory (2,20,23–29). The BASDAI consists of 6 questions answered on a visual analog scale (VAS) (2). The questions are related to fatigue, back pain, pain and/or swelling of the peripheral joints, localized tenderness, and duration and severity of morning stiffness. The 10-cm horizontal VAS has the labels none = 0 and very severe = 10 at either end for the first 5 questions, and 0 hours = 0 and 2 or more hours = 10 for the duration of morning stiffness. The mean score of the 2 questions on morning stiffness counts as 1 variable. The mean score of the 5 items is the total score. The BASFI contains 10 questions on functional ability, completed on a 10-cm horizontal VAS, with the labels easy = 0 and impossible = 10 at either end (20). The mean of the 10 items is the final score. The BAS-G consists of 2 questions on the effect of AS on well-being over the past week and over the past 6 months, respectively, and is answered on a 10-cm horizontal VAS, with the labels none = 0 and very severe = 10 at either end (21). The mean score of the 2 items is the final score. The ranges of the final score for BASDAI, BASFI, and BAS-G are 0 (best) to 10 (worst).

The SF-36 is a widely applied generic instrument for measuring health status, and consists of 8 domains: physical functioning, social functioning, role limitations (physical problem), role limitations (emotional problem), mental health, vitality, bodily pain, and general health perceptions (22). Scores range from 0 (worst) to 100 (best).

Patients participating in the spa therapy trial and the OASIS cohort study also completed a disease-specific quality of life questionnaire (ASQoL) (30), and the VAS question from the EuroQoL (EQ-$5D_{VAS}$) on a person's overall perceived health (31). The ASQoL is a newly developed disease-specific quality of life instrument containing 18 yes/no questions (30). Scores range from 0 to 18, with lower scores implying a better quality of life. EQ-$5D_{VAS}$ scores range from 0 to 100, with higher scores implying better health.

The question, "Which factors increase your fatigue due to AS?" was administered only to the 124 OASIS patients and could be answered by the terms pain, stiffness, problems with a good sleep posture, the weather, exercise, poor sleep, work, medication, none of these factors, or other factors (with space to write down any factors). Multiple answers were allowed.

Comorbidity was assessed in the SDR and OASIS studies by asking patients to select comorbid diseases from a list provided in the questionnaire or to add diseases not included in the list.

Statistical analysis. Patients pooled from all 3 sources were divided into 2 groups. Patients with scores > 5.0 on the BASDAI fatigue question were labeled as experiencing fatigue as a major symptom (F+). Patients with scores < 5.0 were labeled as experiencing fatigue as a minor symptom (F−). Data from the patients scoring exactly 5.0 on the first BASDAI question were omitted. The data were reanalyzed with other cutoff points (F− group < 4.0, F+ group > 6.0), but the results were similar (data not shown).

Student's *t*-tests were applied to compare continuously distributed characteristics between the F+ and F− groups. Dichotomous variables were analyzed by chi-square testing.

To define reproducibility of the BASDAI fatigue question and the dimensions of the MFI, intraclass correlation coefficients (ICCs) were calculated for the control arm of the spa therapy trial, with a 6-week interval between the measurements without change of therapy. ICCs > 0.75 were considered acceptable (32).

Responsiveness of the BASDAI fatigue question and the dimensions of the MFI were determined by 3 different methods: the effect size (ES) (33), the standardized response mean (SRM) (34), and the method described by Guyatt (35). The results were interpreted according to Cohen's effect size index, in which 0.2 refers to a small change, 0.5 to a moderate change, and 0.8 or more to a large change (36). The ES is calculated as the mean change after treatment compared with baseline, divided by the standard deviation (SD) of the baseline scores (33). The SRM is calculated as the mean change after treatment compared with baseline, divided by the SD of the change score (34). The method described by Guyatt is calculated as the mean change score in the treatment group divided by the SD of the change score in the control group (35).

The distribution of factors believed to influence fatigue in F+ and F− patients was analyzed by chi-square testing. Pearson's correlations were used to determine the relationship between both the BASDAI fatigue question and the dimensions of the MFI with other questionnaires. Logistic regression analysis was used to assess which factors were associated with fatigue in patients with AS. Independent variables comprised age, sex, disease duration, comorbidity, mental health status (measured with the mental health domain from the SF-36), and the disease-specific measures of the BASDAI (without the fatigue question), BASFI, and BAS-G.

Multiple regression analysis was used to investigate whether fatigue contributes in explaining quality of life, independent of demographic and disease-related factors. Dependent variables were the dimensions of the SF-36 separately, and the ASQoL. Independent variables were either the BASDAI fatigue question (VAS score) or the 5 dimensions of the MFI. Adjustments were made for age, sex, comorbidity, disease duration, mental health status, and BASFI. Because the BASDAI (without fatigue), BASFI, and BAS-G showed a high level of collinearity (tolerance < 0.4), only the BASFI score was used as covariate, and BASDAI and BAS-G were excluded.

RESULTS

Table 2 shows the patient characteristics of the total study population and the 3 studies separately. Eighteen patients

Table 2. Patient characteristics of the total study population and the different study groups separately, divided into F+ and F− groups*

	All patients (n = 812)		SDR (n = 568)		Spa therapy trial (n = 120)		OASIS (n = 124)	
	F+ (n = 415)†	F− (n = 361)†	F+ (n = 290)	F− (n = 247)	F+ (n = 72)	F− (n = 44)	F+ (n = 53)	F− (n = 70)
Men, %	67‡	74‡	67‡	75‡	71	75	66	69
Age, years	45 ± 9	45 ± 11	44 ± 9	43 ± 10	47 ± 10	50 ± 10	48 ± 11	49 ± 12
Disease duration, years	12 ± 8	13 ± 8	12 ± 8	13 ± 8	11 ± 6	11 ± 6	14 ± 10	15 ± 8
Duration of complaints, years	22 ± 12	23 ± 11	na	na	18 ± 9	18 ± 9	27 ± 13	26 ± 11
Patients with comorbidity, %	48§	33§	50§	33§	na	na	40	33

* Mean ± SD. F+ = fatigue score on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >5.0; F− = fatigue score on BASDAI <5.0 (data from 18 patients scoring exactly 5.0 as well as 18 patients with missing data on the BASDAI fatigue question are omitted from the F+ and F− groups); SDR = Standardized Diagnosis Register of Rheumatic Diseases; OASIS = Observational Study on Outcome in Ankylosing Spondylitis; na = data not available.
† Patient characteristics are calculated on available data.
‡ $P < 0.05$ between F+ and F− groups.
§ $P < 0.001$ between F+ and F− groups.

(14 from the SDR study and 4 from the spa therapy trial) were excluded, because they answered exactly 5.0 on the BASDAI fatigue question. An additional 18 patients (17 from the SDR and 1 from the OASIS study) did not complete the BASDAI fatigue question and were therefore also excluded. Overall, 53% (415) of the patients were included in the F+ group, and 47% (361) in the F− group. Both groups were similar with respect to age, disease duration, and duration of complaints. Significantly more women and significantly more comorbidity were found in the F+ group compared with the F− group in the total population ($P = 0.043$ and $P < 0.001$, respectively).

Table 3 shows how patients in the F+ and F− groups performed on the MFI and other questionnaires. Patients from the F+ group had significantly worse scores on all questionnaires as compared with the F− group (all $P < 0.001$).

Responsiveness and reproducibility. Six weeks after baseline measurement, and after the intervention had taken place, all patients from the spa therapy trial completed a second questionnaire. Reproducibility was calculated using the results of the control arm (n = 40). The ICCs showed moderate to good concordance: the ICC for the BASDAI fatigue question was 0.60, and the ICC for the MFI dimension "general fatigue" was 0.67, for "physical fatigue" 0.57, for "reduced activity" 0.66, for "reduced motivation" 0.75, and for "mental fatigue" 0.75.

Table 4 shows the scores on the BASDAI fatigue question and on the MFI dimensions of the 3 spa therapy trial arms (n = 40 for each arm). Improvements in the BASDAI fatigue question and in all dimensions of the MFI were observed after spa therapy in both intervention arms compared with controls. However, because arm 1 showed a greater and more prolonged improvement after the intervention compared with arm 2 (consistent with the results on the primary outcomes of the spa therapy trial) (19), we decided to calculate responsiveness scores only for arm 1 with the results at 3 months after spa therapy (time point

Table 3. Scores of the F+ and the F− groups on the dimensions of the MFI and several questionnaires*

Questionnaire (range)	All patients F+ (n = 415)	All patients F− (n = 361)
MFI (4–20)		
General fatigue	15.5 ± 3.3	10.1 ± 3.5
Physical fatigue	14.2 ± 3.3	9.9 ± 3.7
Reduced activity	11.5 ± 4.0	8.6 ± 3.5
Reduced motivation	10.4 ± 3.6	8.0 ± 3.1
Mental fatigue	10.1 ± 4.3	7.8 ± 3.6
BASDAI (0–10)	5.6 ± 1.8	2.4 ± 1.5
BASDAI without fatigue question (0–10)	5.2 ± 2.1	2.5 ± 1.7
BASDAI fatigue question (0–10)	7.4 ± 1.4	2.4 ± 1.5
BASFI (0–10)	5.0 ± 2.2	2.6 ± 2.0
BAS-G (0–10)	5.9 ± 2.1	2.9 ± 2.1
ASQoL (0–18)†	9.6 ± 3.8	4.3 ± 3.4
EQ-5D$_{VAS}$ (0–100)†	53.7 ± 18.3	70.0 ± 14.8
SF-36 (0–100)		
Physical functioning	55.8 ± 23.4	75.6 ± 18.7
Social functioning	64.6 ± 24.6	84.3 ± 19.4
Role limitation (physical)	35.6 ± 38.1	73.4 ± 36.8
Role limitation (emotional)	68.5 ± 41.3	85.8 ± 29.5
Mental health	65.5 ± 18.1	77.3 ± 15.5
Vitality	42.6 ± 16.5	64.5 ± 16.9
Bodily pain	48.3 ± 19.2	69.8 ± 17.9
General health	42.8 ± 20.2	59.9 ± 18.7

* Mean ± SD. MFI = Multidimensional Fatigue Inventory; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BAS-G = Bath Ankylosing Spondylitis Global; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire; EQ-5D$_{VAS}$ = EuroQol visual analog scale; SF-36 = Short Form 36. F+ = fatigue score on the BASDAI >5.0, F− = fatigue score on BASDAI <5.0. See Patients and Methods section for possible score ranges.
† Data available on spa therapy trial and OASIS patients only (F+ n = 125; F− n = 114). All differences between scores in the F+ and F− groups were statistically significant at the 0.001 level.

Table 4. Results from the intervention arms and control arm of the spa therapy trial on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) fatigue question and the dimensions of the Multidimensional Fatigue Inventory before and after the intervention

	BASDAI fatigue question	Multidimensional Fatigue Inventory				
		General fatigue	Physical fatigue	Reduced activity	Reduced motivation	Mental fatigue
Arm 1 (n = 40)						
Baseline	5.6 ± 2.7	13.6 ± 4.0	12.7 ± 4.3	10.8 ± 3.9	9.5 ± 3.3	9.5 ± 5.2
1 week after end spa therapy	5.7 ± 3.4	12.2 ± 5.3	10.6 ± 5.1†	10.1 ± 4.1	8.6 ± 3.2	8.0 ± 4.0*
3 months after end spa therapy	3.2 ± 2.3*	10.2 ± 4.7†	9.2 ± 4.0†	9.7 ± 3.9	7.7 ± 3.0†	7.5 ± 3.9*
Arm 2 (n = 40)						
Baseline	5.9 ± 2.5	14.8 ± 4.7	13.0 ± 5.0	10.9 ± 4.4	8.6 ± 3.2	10.2 ± 4.7
1 week after end spa therapy	5.9 ± 3.1	13.5 ± 5.2	10.6 ± 5.1†	10.4 ± 4.9	8.8 ± 3.8	10.2 ± 4.9
3 months after end spa therapy	4.8 ± 2.7	12.9 ± 4.7	11.4 ± 5.0	9.7 ± 4.1*	8.8 ± 3.5	10.2 ± 5.0
Control arm (n = 40)						
Baseline	5.9 ± 2.7	13.6 ± 4.4	12.0 ± 3.9	10.4 ± 3.6	8.6 ± 3.8	9.2 ± 4.4
1 week	5.3 ± 2.6	13.5 ± 3.7	12.5 ± 4.1	10.6 ± 3.6	8.6 ± 3.5	9.2 ± 4.1
3 months	4.9 ± 2.4	13.3 ± 4.6	12.1 ± 4.1	10.8 ± 4.1	9.0 ± 3.7	9.2 ± 4.6

Mean ± SD. Arm 1 = spa therapy in Austria; Arm 2 = spa therapy in The Netherlands; Control arm = continued standard treatment at home. See Patients and Methods section for possible score ranges.
* $P < 0.05$ compared with controls.
† $P < 0.01$ compared with controls.

of maximum effect) compared with baseline (Table 5). The BASDAI fatigue question showed high responsiveness with all 3 methods. For the MFI, the highest responsiveness was found for the dimensions "general fatigue" and "physical fatigue" irrespective of the method. The other dimensions showed moderate responsiveness scores.

Factors influencing and associated with fatigue. More than 50% of all 124 OASIS patients associated fatigue with pain (70%) and stiffness (54%) (Table 6). The factors perceived to be associated with fatigue, and presented in a hierarchical order, were grossly similar in the F+ and F− groups, but pain, poor sleep, and work were significantly more often considered important in the F+ group.

The scores of 5 disease-specific questionnaires as well as the EQ-$5D_{VAS}$, and all dimensions of the SF-36 were significantly correlated with the BASDAI fatigue question and all dimensions of the MFI separately (Table 7). No major differences in correlations between these questionnaires and either the BASDAI fatigue question or the "general fatigue" and "physical fatigue" dimensions of the MFI were found. The dimensions "reduced activity," "reduced motivation" and "mental fatigue" were correlated to a lesser degree. When using the "vitality" domain of the SF-36 as an external validation to measure fatigue, similar correlations were found between the above-mentioned questionnaires and the "vitality" domain, confirming the robustness of the results (data not shown).

To investigate which domains of the MFI contributed independently in explaining "fatigue" as elicited by the BASDAI fatigue question, logistic regression analysis was performed with F+/F− (n = 812) as dependent variable, and the 5 MFI dimensions as well as age, sex, and disease duration as explanatory variables. General fatigue ($P < 0.001$), physical fatigue ($P = 0.02$), reduced activity ($P = 0.042$), and reduced motivation ($P = 0.008$) were independently associated with F+/F−, whereas mental fatigue ($P = 0.93$) was not. This confirmed the hypothesis that fatigue is a multidimensional attribute.

In a separate logistic regression analysis (n = 776), the scores of the disease-specific questionnaires BASDAI (without fatigue), BASFI and BAS-G were assessed for their independent association with F+/F−, after controlling for age, sex, comorbidity, mental health status, and

Table 5. Responsiveness of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) fatigue question and the dimensions of the Multidimensional Fatigue Inventory calculated with 3 different responsiveness methods*

	BASDAI fatigue question	Multidimensional Fatigue Inventory				
		General fatigue	Physical fatigue	Reduced activity	Reduced motivation	Mental fatigue
Effect size	0.89	0.82	0.81	0.28	0.54	0.38
Standardized response mean	0.89	0.70	0.82	0.23	0.51	0.49
Guyatt method	0.92	0.86	0.96	0.30	0.50	0.57

* For calculation of the different responsiveness methods see Patients and Methods section of the text. Responsiveness was measured with the data of the patients from arm 1 of spa therapy trial (n = 40). Positive changes imply improvement.

Table 6. Factors influencing fatigue in the opinion of the patients from the OASIS study*

	All patients (n = 124)	F+ (n = 53)	F− (n = 70)	*P* (χ^2 test)
Pain	87 (70)	44 (83)	42 (60)	0.011
Stiffness	67 (54)	31 (58)	35 (50)	0.456
Weather	55 (44)	28 (53)	26 (37)	0.128
Poor sleep	49 (40)	30 (57)	18 (26)	<0.001
Sleep posture	45 (36)	24 (45)	20 (29)	0.088
Work	27 (22)	19 (36)	8 (11)	0.003
Exercises	10 (8)	5 (9)	4 (6)	0.667
Medication	9 (7)	5 (9)	4 (6)	0.667
None of these factors	2 (2)	0 (0)	2 (3)	0.603
Other factors	0 (0)	0 (0)	0 (0)	—

* Absolute number (%) of patients. Multiple answers were allowed. OASIS = Observational Study on Outcome in Ankylosing Spondylitis.

disease duration (Table 8). The BASDAI-, BASFI-, and BAS-G scores, mental health status, and age were selected as independently associated with fatigue. The age effect was only marginally statistically significant, suggesting that fatigue mainly relates to disease activity, functional ability, global well-being, and mental health status. In a multiple regression analysis model with the "vitality" domain of the SF-36 as the dependent factor, similar results were found (data not shown).

Fatigue and quality of life. Multiple regression analysis was used to assess whether fatigue contributed in explaining quality of life, as assessed by dimensions from the SF-36 and the ASQoL, after controlling for age, sex, comorbidity, disease duration, mental health status, and BASFI (n = 776). Dependent variables of the SF-36 were physical functioning, social functioning, vitality, bodily pain, and general health, respectively. Role limitation (physical) and role limitation (emotional) were excluded, because neither was normally distributed, nor after log transformation. Mental health was excluded as a dependent variable, because this was used in the analyses as an independent variable to control for mood disorders.

Fatigue as elicited by the BASDAI fatigue question was significantly associated with all separate dimensions of the SF-36 studied and with the ASQoL (Table 9). Fatigue as elicited by the MFI was related to quality of life in a different pattern. Different aspects of fatigue (measured with the 5 MFI dimensions) explained different domains of quality of life measured with the SF-36 (Table 9).

Table 7. Correlations between several questionnaires and both the BASDAI fatigue question and dimensions of the Multidimensional Fatigue Inventory

	BASDAI fatigue question	Multidimensional Fatigue Inventory				
		General fatigue	Physical fatigue	Reduced activity	Reduced motivation	Mental fatigue
BASDAI	0.79	0.60	0.61	0.44	0.37	0.33
BASDAI without fatigue question	0.67	0.51	0.56	0.40	0.34	0.31
BASFI	0.57	0.51	0.60	0.45	0.37	0.28
BAS-G	0.68	0.56	0.63	0.44	0.37	0.32
ASQoL*	0.67	0.71	0.73	0.59	0.47	0.46
EQ-5D$_{VAS}$*	−0.53	−0.52	−0.60	−0.41	−0.36	−0.25
SF-36						
Physical functioning	−0.51	−0.47	−0.59	−0.44	−0.35	−0.28
Social functioning	−0.49	−0.49	−0.55	−0.52	−0.42	−0.39
Role limitation (physical)	−0.52	−0.50	−0.51	−0.42	−0.29	−0.30
Role limitation (emotional)	−0.29	−0.31	−0.32	−0.37	−0.27	−0.35
Mental health	−0.40	−0.44	−0.42	−0.47	−0.49	−0.49
Vitality	−0.64	−0.73	−0.65	−0.59	−0.53	−0.42
Bodily pain	−0.59	−0.53	−0.60	−0.45	−0.36	−0.28
General health	−0.48	−0.53	−0.64	−0.45	−0.39	−0.30

* Correlations were measured in the entire study population (n = 812), except for the ASQoL and EQ-5D$_{VAS}$, for which data of spa therapy trial and OASIS patients only were available (n = 244). All correlations were significant at the 0.01 level. BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BAS-G = Bath Ankylosing Spondylitis Global; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire; EQ-5D$_{VAS}$ = EuroQol visual analog scale; SF-36 = Short Form 36; see Table 2 for other definitions.

Table 8. Logistic regression model for explaining fatigue

Variable	RR	95% CI	*P*
BASDAI (without fatigue)	1.47	1.28–1.69	<0.001
BAS-G	1.34	1.19–1.50	<0.001
BASFI	1.16	1.03–1.31	0.018
Mental health	0.98	0.97–1.00	0.012
Age	0.98	0.95–1.00	0.046
Sex	1.12	0.71–1.76	0.627
Disease duration	0.99	0.96–1.01	0.294
Co-morbidity	0.84	0.53–1.31	0.435

The data of the SDR and OASIS study were used (n = 776). Dependent variable: F+/F− group. All independent variables were entered simultaneously into the model. $R^2 = 0.52$. RR = relative risk; CI = confidence interval. See table 7 for additional abbreviations.

DISCUSSION

Fatigue has been described as a major symptom in AS, with up to 65% of the patients reporting it (1–4). In the present study 53% of all patients experienced fatigue, defined as a BASDAI fatigue score of > 5.0.

We assessed the properties of both the single-item BASDAI fatigue question and a multidimensional fatigue questionnaire, the MFI. The advantage of a single question is that it is easy to complete. Important disadvantages are that detailed information is lost with respect to the type of fatigue, and that it does not take into account differences in fatigue experience (12). The advantage of a multidimensional questionnaire is that it deals with different aspects of fatigue, i.e., it provides a profile of fatigue.

Within the field of rheumatology, the MFI has been used to investigate fatigue in patients with primary Sjögren syndrome compared with patients with rheumatoid arthritis (RA) and healthy controls (37). No differences in fatigue scores between patients with primary Sjögren syndrome and RA were found, and both groups reported significantly more fatigue than healthy controls. Depression appeared to be an important confounder. After controlling for depression, significant differences with respect to the dimensions "reduced motivation," and "mental fatigue" disappeared between the patient groups and healthy controls. In the present study, a specific questionnaire to measure depression was not administered to the patients. To address this issue, we controlled for mood disorders in the regression analyses by using the mental health domain from the SF-36. However, analyses with and without the mental health domain as an independent factor were not substantially different (data not shown).

The reproducibility of the BASDAI fatigue question and each dimension of the MFI was moderate to good according to accepted standards, and more or less similar for both questionnaires. However, the ICCs never exceeded 0.75. This might be due to the relatively long interval between the measurements (6 weeks). Although reproducibility was measured in a group of patients presumed to be stable, it may have been influenced by fluctuating behavior of fatigue in AS. The responsiveness of the BASDAI fatigue question and of each dimension of the MFI was moderate to good, and comparable for both instruments (Table 5). From the present study it can be concluded that the BASDAI fatigue question and the MFI have equal properties with respect to reproducibility and responsiveness.

The patients reported a considerable number of factors that, in their opinion, were associated with fatigue. More than 50% of the patients reported that pain and stiffness negatively influenced their fatigue. Fatigue due to pain may be explained by several mechanisms (38). Dealing with pain may require both mental and physical energy, more energy may be necessary to perform daily tasks in a less painful way, and pain may cause sleep disturbances with consequent daytime fatigue. Except for pain, poor sleep, and work, however, none of the other factors studied discriminated between the F+ and F− groups. In a study by Jones et al the weather was reported most often by AS patients to negatively influence fatigue (3). Exercises were reported to have an increasing effect on fatigue by 37% of the strongly fatigued patients, and by 10% of the less fatigued patients. In our study, exercises were not reported to be of substantial negative influence on fatigue by both groups. Contrary, the level of fatigue had de-

Table 9. Multiple regression analyses to study whether fatigue, measured with either the BASDAI fatigue question or the dimensions of the MFI, contributes in explaining quality of life as assessed by the SF-36 and the ASQoL

Dependent variable*	BASDAI fatigue question	Multidimensional Fatigue Inventory				
		General fatigue	Physical fatigue	Reduced activity	Reduced motivation	Mental fatigue
SF-36						
Physical functioning	−0.061†	0.139	−1.119§	−0.413†	0.589‡	0.123
Social functioning	−0.066†	−0.003	−0.522	−0.936§	0.265	0.121
Vitality	−0.258§	−1.875§	−0.346	−0.488‡	−0.516‡	0.138
Bodily pain	−0.179§	−0.458†	−1.082§	−0.062	0.010	0.244
General health	−0.118§	−0.082	−2.045§	−0.118	−0.129	0.260
ASQoL	0.055§	0.261§	0.226‡	0.038	−0.040	−0.039

Beta coefficients are shown for each of the models.
* Dependent variables were 5 of the 8 dimensions of the SF-36 separately, and the ASQoL. Independent variables were either the BASDAI fatigue question or the five MFI dimensions. Adjustments were made for age, gender, comorbidity, disease duration, mental health status, and Bath Ankylosing Spondylitis Functional Index score. For the separate dimensions of the SF-36, the data of the SDR and OASIS study (n = 776) were used; for the ASQoL, only data of the OASIS study were available (n = 124). See table 7 for abbreviations.
† $P = < 0.05$, ‡ $P = < 0.01$, § $P = < 0.001$

creased after a 3-week course of spa therapy with an intensive physical exercise program (Table 4). Patients who were strongly fatigued before the intervention did not show a worsening of the symptoms after the spa therapy. In contrast, they showed more improvement in fatigue than the patients from the F− group (data not shown).

Fatigue implicitly appeared to be related to disease activity, functional ability, global well-being, mental health status, and age, explaining 52% of the variance. In agreement with these findings, Jones et al found that pain, stiffness, and functional ability were significantly associated with the level of fatigue, explaining 42% of the variance (3). In the study by Jones and colleagues, age was not significantly associated with fatigue. In the present study, the age effect was only marginally statistically significant, and not considered clinically relevant. The pain and stiffness components of Jones' study were incorporated in our study in the BASDAI, and therefore not selected separately. Global well-being and mental health status were not entered into the regression models by Jones et al, but were found to be important factors in explaining fatigue in our study.

The final aim of the study was to investigate whether fatigue contributes in explaining quality of life. Scores on the BASDAI fatigue question were significantly associated with scores on several dimensions of the SF-36 and with the ASQoL, suggesting that quality of life is influenced by the degree of fatigue. Multiple regression analysis further suggested that different aspects of fatigue explained different domains of quality of life. Such an interrelationship is missed if a single-item questionnaire is used. This differential assessment of various aspects of the SF-36 further validates the MFI.

In conclusion, fatigue as a major symptom of AS can appropriately be measured with both a single-item question on the intensity of fatigue, and with the MFI. The MFI, however, provides more insight into specific dimensions of fatigue. Fatigue appears to be associated with the level of disease activity, functional ability, global well-being, and mental health status. In addition, fatigue negatively influences different aspects of quality of life.

ACKNOWLEDGMENTS

We gratefully thank all rheumatologists and their assistants from the following rheumatology centers that participate in the Dutch Standardized Diagnosis Register of Rheumatic Diseases: Sint Antoniusziekenhuis Nieuwegein, Rode Kruisziekenhuis Den Haag, Bosch Medisch Centrum Den Bosch, Sint Laurentiusziekenhuis Roermond, Sint Jansgasthuis Weert, Groene Hartziekenhuis Gouda, Albert Schweitzerziekenhuis locaties Amstelwijck en Dordwijk Dordrecht, Kennemer Gasthuis locatie Deo Haarlem, Lievensberg Ziekenhuis Bergen op Zoom, Tweesteden Ziekenhuis Tilburg, Rijnstate Ziekenhuis Arnhem, St. Maartenskliniek Nijmegen, Medisch Spectrum Twente Enschede, and Academisch Ziekenhuis Maastricht.

REFERENCES

1. Calin A, Edmunds L, Kennedy LG. Fatigue in ankylosing spondylitis: why is it ignored? J Rheumatol 1993;20:991–5.
2. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
3. Jones SD, Koh WH, Steiner A, Garrett SL, Calin A. Fatigue in ankylosing spondylitis: its prevalence and relationship to disease activity, sleep, and other factors. J Rheumatol 1996;23: 487–90.
4. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999; 12:247–55.
5. Belza B. The impact of fatigue on exercise performance. Arthritis Care Res 1994;7:176–80.
6. Piper BF, Lindsey AM, Dodd MJ, Ferketich S, Paul SM, Weller S. The development of an instrument to measure the subjective dimension of fatigue. In: Funk SG, Tournquist EM, Champagne MT, Copp LA, Weise RA, editors. Key aspects of comfort: management of pain, fatigue, and nausea. New York: Springer; 1989. p. 199–208.
7. Belza Tack B. Self-reported fatigue in rheumatoid arthritis: a pilot study. Arthritis Care Res 1990;3:154–7.
8. Aaronson LS, Teel CS, Cassmeyer V, Neuberger GB, Pallikkathayil L, Pierce J, et al. Defining and measuring fatigue. Image J Nurs Sch 1999;31:45–50.
9. Tiesinga LJ, Dassen TW, Halfens RJ. Fatigue: a summary of the definitions, dimensions, and indicators. Nurs Diagn 1996;7: 51–62.
10. Van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis: progress report of the ASAS Working Group. J Rheumatol 1999;26:951–4.
11. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18 Suppl 1:S79–83.
12. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.
13. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995;22:639–43.
14. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum 1998;25: 677–84.
15. Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. Br J Cancer 1996;73:241–5.
16. Schneider RA. Reliability and validity of the Multidimensional Fatigue Inventory (MFI-20) and the Rhoten Fatigue Scale among rural cancer outpatients. Cancer Nurs 1998;21: 370–3.
17. Meek PM, Nail LM, Barsevick A, Schwartz AL, Stephen S, Whitmer K, et al. Psychometric testing of fatigue instruments for use with cancer patients. Nurs Res 2000;49:181–90.
18. Miedema HS, van der Linden SM, Rasker JJ, Valkenburg HA. National database of patients visiting rheumatologists in The Netherlands: the Standard Diagnosis Register of Rheumatic Diseases: a report and preliminary analysis. Br J Rheumatol 1998;37:555–61.
19. Van Tubergen A, Landewé R, van der Heijde D, Hidding A, Wolter N, Asscher M, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum (Arthritis Care Res) 2001;45:430–8.
20. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
21. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol 1996;35:66–71.
22. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form

health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
23. Ward MM, Kuzis S. Validity and sensitivity to change of spondylitis-specific measures of functional disability. J Rheumatol 1999;26:121–7.
24. Ruof J, Stucki G. Comparison of the Dougados Functional Index and the Bath Ankylosing Spondylitis Functional Index: a literature review. J Rheumatol 1999;26:955–60.
25. Spoorenberg A, van der Heijde D, de Klerk E, Dougados M, de Vlam K, Mielants H, et al. A comparative study of the usefulness of the Bath Ankylosing Spondylitis Functional Index and the Dougados Functional Index in the assessment of Ankylosing Spondylitis. J Rheumatol 1999;26:961–5.
26. Calin A, Nakache JP, Gueguen A, Zeidler H, Mielants H, Dougados M. Outcome variables in ankylosing spondylitis: evaluation of their relevance and discriminant capacity. J Rheumatol 1999;26:975–9.
27. Ruof J, Sangha O, Stucki G. Comparative responsiveness of 3 functional indices in ankylosing spondylitis. J Rheumatol 1999;26:1959–63.
28. Calin A, Nakache JP, Gueguen A, Zeidler H, Mielants H, Dougados M. Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? Rheumatology (Oxford) 1999;38:878–82.
29. Van Tubergen A, Debats I, Ryser L, Londono J, Burgos-Vargas R, Cardiel MH, et al. The use of a numerical rating scale as an answer modality in ankylosing spondylitis specific questionnaires. Arthritis Rheum (Arthritis Care Res). In press.
30. Helliwell P, Doward L, Whalley D, Tennant A, McKenna S, Reynolds S, et al. Psychometric and scaling properties of a new quality of life instrument specific to ankylosing spondylitis (AS) [abstract]. Arthritis Rheum 1999;42 Suppl 9:572.
31. The EuroQoL Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16: 199–208.
32. Streiner D, Norman G. Health measurement scales: a practical guide to their development and use. Oxford: Oxford University Press; 1989.
33. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27 Suppl 3:S178–89.
34. Liang MH, Fossel AH, Larson MG. Comparisons of five health status instruments for orthopedic evaluation. Med Care 1990; 28:632–42.
35. Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987;40:171–8.
36. Cohen J. Statistical power analysis for behavioral sciences. 2nd ed. Hillsdale (NY): Lawrence Erlbaum Associates; 1988.
37. Barendregt PJ, Visser MR, Smets EM, Tulen JH, van den Meiracker AH, Boomsma F, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291–5.
38. Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993;42:93–9.