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ORIGINAL REPORT

EXPLANATORY FACTORS AND PREDICTORS OF FATIGUE IN PERSONS WITH RHEUMATOID ARTHRITIS: A LONGITUDINAL STUDY

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Objective: **To investigate the impact of disease-related aspects on long-term variations in fatigue in persons with rheumatoid arthritis.**

Design: **Observational longitudinal study.**

Methods: **Sixty-five persons with rheumatoid arthritis, age range 20–65 years, were invited to a clinical examination at 4 time-points during the 4 seasons. Outcome measures were: general fatigue rated on visual analogue scale (0–100) and aspects of fatigue assessed by the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire. Disease-related variables were: *disease activity* (erythrocyte sedimentation rate), *pain threshold* (pressure algometer), *physical capacity* (six-minute walk test), *pain* (visual analogue scale (0–100)), *depressive mood* (Hospital Anxiety and Depression scale, depression subscale), *personal factors* (age, sex, body mass index) and *season*. Multivariable regression analysis, linear mixed effects models were applied.**

Results: **The strongest explanatory factors for all fatigue outcomes, when recorded at the same time-point as fatigue, were pain threshold and depressive mood. Self-reported pain was an explanatory factor for physical aspects of fatigue and body mass index contributed to explaining the consequences of fatigue on everyday living. For predicting later fatigue pain threshold and depressive mood were the strongest predictors.**

Conclusion: **Pain threshold and depressive mood were the most important factors for fatigue in persons with rheumatoid arthritis.**

Key words: fatigue; rheumatoid arthritis; longitudinal study; outcome assessment.

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INTRODUCTION

Pharmacological treatment of rheumatoid arthritis (RA) has improved substantially over the last decade, contributing to better control of inflammation, reduced joint damage and improved maintenance of function (1). However, despite adequate pharmacological treatment, many persons with RA report that they experience fatigue. This has been noticed increasingly and has become established as one of the most important issues in rheumatology, from the perspective of the patients (2). After pain, fatigue is the most prominent symptom of the disease, and for many patients it has greater impact on daily life than pain (3).

The prevalence of fatigue in persons with RA varies in different investigations, from 42% to 80%, and the prevalence of severe fatigue is approximately 50% (4). Persons with RA describe fatigue as multidimensional with physical, cognitive and emotional components (3, 5).

Although fatigue is commonly reported in RA, little is known about its causes and consequences (6). A conceptual model for understanding fatigue in RA proposes that fatigue is influenced by an interaction between disease processes, thoughts, feelings and behaviours, and personal life issues (7). A subsequent review suggested that factors contributing to fatigue would be found among disease-related aspects, such as pain, inflammatory activity, physical functioning, cognitive/emotional functioning and social/environmental aspects (6). However, none of these variables show profound and stable relationships with fatigue across studies. For example, 5 of 6 studies reporting clinical characteristics of inflammatory activity (e.g. erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)) showed no association with fatigue (6). The strongest associations with fatigue were found with pain, disability/physical functioning and depression/depressive mood (6).

Pain is a core symptom in RA and many patients continue to have pain when inflammation has declined (8). At joint site, pain threshold, i.e. the degree of pressure eliciting pain, is found to be lower in persons with RA than in healthy controls, and sleep problems are found to be related to pain and pain threshold (9, 10).

Most studies investigating associations with fatigue have been cross-sectional and have applied a global rating scale, such as a one-dimensional visual analogue scale (VAS), for measuring fatigue (6). Due to the multidimensional nature of

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fatigue, several aspects, such as physical and mental aspects, are recommended for evaluating fatigue (6). It appears that measures of one-dimensional or multiple aspects of fatigue are useful in different contexts (11).Therefore, longitudinal studies that measure both one-dimensional and multiple aspects of fatigue (6) regularly over time (4) are necessary to yield more knowledge about fatigue. To the best of our knowledge no such study has been published.

The aim of this study was to investigate how disease-related aspects contribute to the variation in general fatigue, as well as in multiple aspects of fatigue, in persons with RA at 4 time-points during the 4 seasons, using multivariable regression analysis.

METHODS

Participants

Participants were identified by the hospital administrative register at the rheumatology clinic, Sahlgrenska University Hospital, Gothenburg, Sweden.

Inclusion criteria were: diagnosis of RA according to the International Classification of Diseases 10 (diagnosis codes M05 and M06) (12); of working age (20–65 years); disease duration > 3 years; and stable pharmacological treatment > 3 months prior to study entry concerning disease modifying anti-rheumatic drugs (DMARDs) including biological DMARDS and glucocorticosteroids. Exclusion criteria were: other severe somatic or psychiatric diseases or not having the capacity to communicate effectively in Swedish.

Persons with RA, with a diagnosis code, fulfilling the age criterion and with a visit to the clinic in the last 1.5 years were recruited. Of these, 250 persons were randomly selected and inclusion and exclusion criteria were checked from the medical records. If eligible, a letter with an invitation to participate in the study was sent to the persons ($n = 140$). A total of 72 persons (51%) answered the invitation letter and, of those, 65 persons entered the study (7 out of 72 declined to participate because of: other health problems $n = 3$, no time $n = 2$, family reasons $n = 1$, to much effort $n = 1$). Three persons, 65 years of age at the time of recruitment had turned 66 years when entering the study. Ninety-one percent ($n = 61$) of subjects participated in > 50% of the measurements.

Measures

Demographic data, including age, sex, disease duration, medication, work status and body mass index (BMI), were obtained by a standardized interview.

Clinical examination included:

- *Disease activity,* assessed by disease activity score, DAS-28 (13) based on the number of tender and swollen joints (0–28), patient global assessment of general health (VAS 0–100 mm) and ESR.
- *Pain threshold,* assessed using a pressure algometer (Somedic Sales AB, Hörby, Sweden) with 1 cm^2 probe area and a pressure increase of approximately 50 kPa/s (14). Pain thresholds were measured in kPa and assessed bilaterally in the upper and lower limb (thumb nail base; m. trepezius; m. supraspinatus; knee m. vastus medialis; and m. gluteus). A mean value of the 10 locations assessed was calculated.
- *Physical capacity* assessed by the six-minute walk test (6MWT), measuring the walking distance, in m, during 6 min (15).

Self-reported questionnaires included:

- *General fatigue* rated on a one-dimensional VAS (0–100 mm) during the last week, with anchors "no fatigue" and "worst imaginable fatigue".
- *Multiple aspects of fatigue* rated on the Bristol Rheumatoid Arthritis Fatigue–Multi-dimensional Questionnaire (BRAF-MDQ) (Swedish version) (16, 17). The summa-score "Total" measures general fatigue (0–70) and the 4 sub-scores are "Physical" (0–22; a measure of physical fatigue), "Living" (0–21; describing sequelae due to the unpredictability of fatigue), "Cognition" (0–15; describing the cognitive effects of fatigue) and "Emotion" (0–12; describing the effects of fatigue on emotions and mood). A higher score denotes more severe fatigue.
- *Self-reported pain* rated on VAS (0–100 mm) during last week, with anchors "no pain" and "worst imaginable pain".
- *Depressive mood* rated on the Hospital Anxiety and Depression scale, depression subscale HADS-D (0–21). A score ≥ 11 indicates probable depression and a score ≥ 8 indicates possible depression (18).
- *Functional status (disability)* rated on the Swedish version of Health Assessment Questionnaire (HAQ) range 0–3. A score ≤ 1.0 is regarded as indicating a low level of disability (19).

Procedure

All participants were invited to a clinical examination at 4 time-points during the course of the study, approximately 3 months apart, to cover the 4 seasons. At these time-points demographic data, disease activity, inflammation parameters, pain thresholds and physical capacity were assessed and self-reported questionnaires to measure the level of fatigue and other health aspects in RA were administered.

The primary objective of this study was to analyse whether disease activity, physical capacity, pain, pain thresholds, depressive mood, age, sex, body mass index (BMI) and season, explain variations in fatigue over time. Variables recorded at the same time-point as the fatigue scorings of the participants were used as explanatory factors of fatigue. Variables measured at the previous time-point, approximately 3 months previously, were used as predictors of fatigue.

The study was approved by the Regional Ethical Review Board in Gothenburg. Written and oral information were given to all participants and written consent was obtained from all participants.

Trial registration. ClinicalTrials.gov Identifier NCT01697202.

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD), median (max; min) or number (n) and percentage for demographic data.

Correlation analyses using Pearson's correlation coefficient were made for the independent variables to test for risk of collinearity ($r \geq 0.7$). Due to risk of collinearity, *disease activity* measured with DAS-28 was omitted from the regression analysis in favour of ESR.

Multivariable regression analysis, the linear mixed effects model, was used to analyse the outcome fatigue, with the 4 time-points included as an explanatory variable (factor). The regression model was specified to have a random intercept to handle the repeated measurements over time (20). In the linear mixed effect model all measured values are used and missing values do not lead to exclusion of any measured data. The selected fixed variables were: *ESR, VAS pain, Algometer, 6MWT and HADS-D*. Also the personal factors *Age, BMI,* and *Sex* were included in the analyses as well as *Season*. *Sex* and *Season* were included as factors, *Sex* was defined as female and male, and *Season* was defined as winter (December, January, February), spring (March, April, May), summer (June, July, August) and autumn (September, October, November). The other variables were included as continuous variables.

Two analyses were tested: (*i*) explanatory factors for fatigue with variables and outcome recorded at the same time-point; (*ii*) predictors of fatigue with variables recorded at the time-point prior to the outcome (approximately 3 months). In both analyses, longitudinal data with measures at repeated time-points were analysed according to the model building procedure described below.

To identify important variables a process of model building steps were performed similar to the steps proposed earlier for logistic regression (21). As a first step, to determine which variables to include in the multivariable regression analysis full model, univariate analyses

Table I. *Demographic data of the 65 persons with rheumatoid arthritis at baseline*

Variables	Mean (SD)	Median (min;max)	*n* (%)
Age, years	53.7 (9.9)	56 (23;66)	
Sex, female			48 (74)
Disease duration, years	15.3 (9.6)	12 (4;45)	
BMI, kg/m^2	26.7 (5.2)	26 (19;42)	
DAS 28	3.7 (1.4)	3.8 (0.8;6.9)	
Tender joints 0–28	6.9 (6.5)	5 (0;27)	
Swollen joints 0–28	3.7 (3.5)	3 (0;13)	
Erythrocyte sedimentation rate, mm	10.8 (10.2)	7 (2;53)	
General health, VAS 0–100, mm	36.4 (22.7)	32 (1;83)	
HAQ 0–3	0.6 (0.6)	0.6 (0;2.4)	
Medication			
No DMARD			8 (12)
Conventional synthetic DMARD			57 (88)
Biological DMARD			15 (23)
NSAID			43 (66)
Painkiller			25 (38)
Antidepressive drug			2 (3)
Work status			
Working or studying (full-time or part-time)			41 (63)
Unemployed			7 (11)
Retired			6 (9)
Disability benefits (full-time or part-time)			24 (37)
Parent's allowance			2 (3)

VAS: visual analogue scale; BMI: body mass index; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying anti rheumatic drug; NSAID: non-steroidal anti-inflammatory drugs.

were performed with each independent variable one at a time. Variables with $p < 0.25$ using F-test were included in the multivariable regression analysis full model. In the multivariable analysis full model variables with $p \geq 0.25$ using *t*-test were excluded, resulting in a reduced model. To determine which variables to include in a best-fitting final model the reduced model was compared with the full model and the excluded variables from the full model and the variables with high *p*-value in the univariate regression analyses were reinserted one by one in the reduced model and tested once again. This model building procedure was performed separately for all the outcome variables (VAS fatigue, BRAF-MDQ total score and the 4 subscores).

Estimates with 95% confidence intervals, are presented for the variables included in the final multivariable models.

The variance explained by the final models is presented as 2 ratios; 1 for the residual variance and 1 for the between-individual variance (22). The explained residual variance, denoted R^2_{resid}, is the ratio between the difference between the residual variance in the final model and the model only including random intercept, divided by the residual variance in the model only including random intercept. The explained between-individual variance, denoted $R^2_{between\text{-}ind}$, is the difference between the between-individual variance in the final model and the model only including random intercept, divided by the between-individual variance in the model only including random intercept.

Statistical analyses was performed using SPSS version 15.0 (SPSS Inc., IBM, Chicago USA).

RESULTS

Descriptive statistics of the baseline characteristics of the 65 persons participating in the study are shown in Table I. The mean age and standard deviation (SD) of the participants was 54 years (SD 9.9) , with disease duration of 15 years (SD 9.6), and 74% were women. Baseline fatigue ranged from no fatigue to maximum fatigue (see Table II). Medication at baseline is shown in Table I. During the course of the study 6 participants increased the dosage of, or added, a DMARD, 4 participants changed to another DMARD, and 10 participants decreased the dosage or discontinued a DMARD. Six participants received an intra-articular injection of glucocorticosteroids and 5 participants received short-term use of oral glucocorticosteroids during the investigation. The number of missing values ranges from 0 to 10 in different analyses. No trends were found in missing values in terms of age and symptom severity.

Table II. *Descriptive data of the outcome variable of fatigue, assessed with VAS fatigue and BRAF- MDQ and key explanatory variables, in the 65 persons with RA at the 4 clinical examinations*

	1		2		3		4	
	Mean (SD)	Median (min;max)	Mean (SD)	Median (min;max)	Mean (SD)	Median (min;max)	Mean (SD)	Median (min;max)
Outcome variables								
VAS fatigue (0–100)	47.1 (27.1)	49 (0;100)	49.8 (26.4)	48 (2;98)	50.6 (28.0)	53 (0;98)	46.3 (27.9)	44 (1;94)
BRAF-MDQ								
Total (0–70)	29.0 (14.8)	29 (0;65)	27.0 (12.8)	26 (0;56)	26.2 (13.8)	26 (0;51)	24.3 (14.2)	27 (0;56)
Physical (0–22)	13.9 (5.1)	15 (0;21)	13.8 (4.7)	15 (0;22)	13.6 (5.1)	15 (0;20)	12.5 (5.6)	14 (0;21)
Living (0–21)	6.1 (4.5)	6 (0;21)	5.4 (4.2)	4 (0;16)	5.0 (4.0)	5 (0;14)	4.6 (4.0)	4 (0;16)
Cognitive (0–15)	5.3 (4.0)	5 (0;15)	4.6 (3.6)	4 (0;15)	4.6 (3.5)	5 (0;13)	4.3 (3.5)	4 (0;14)
Emotion (0–12)	3.6 (3.1)	3 (0;12)	3.2 (2.8)	3 (0;12)	2.9 (3.1)	2 (0;11)	2.9 (3.1)	3 (0;11)
Explanatory variables								
ESR (mm)	10.8 (10.2)	7 (2;53)	11.3 (10.1)	8 (2;48)	11.5 (11.1)	8 (2;56)	11.6 (10.1)	10 (1;50)
VAS Pain (0–100)	38.0 (25.5)	34 (0;100)	34.4 (24.8)	30 (1;100)	37.2 (25.2)	35 (0;84)	36.5 (27.7)	32 (0;97)
Algometer, kPa	301.2 (119.0))	281 (95;650)	301.0 (114.8)	272 (153;593)	304.8 (121.9)	278 (85;662)	328.4 (130.9)	283 (103;663)
6MWT, m	535.2 (98.1)	538 (232;775)	544.9 (84.8)	544 (273;704)	537.1 (86.8)	539 (302;727)	537.6 (87.0)	531 (316;699)
HADS-D (7–21)	4.8 (3.8)	4 (0;16)	4.4 (3.6)	3 (0;15)	4.2 (3.5)	4 (0;14)	4.2 (3.5)	3 (0;14)

VAS: visual analogue scale; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire; ESR: erythrocyte sedimentation rate; 6MWT: six-minute walk test; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; SD: standard deviation.

Table III. *Explanatory factors: univariate regression analyses to determine which explanatory factors (*$p < 0.25$*) to include in the multivariable analysis full model*

Explanatory factors	VAS Fatigue	BRAF-MDQ Total	Physical	Living	Cognition	Emotion
ESR	$p=0.328$	$p=0.880$	$p=0.790$	$p=0.696$	$p=0.491$	$p=0.969$
VAS Pain	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.033$**
Algometer	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**
6MWT	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.001$**	**$p=0.031$**	**$p=0.005$**
HADS-D	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**	**$p=0.000$**
Age	$p=0.566$	$p=0.473$	$p=0.567$	$p=0.727$	$p=0.273$	$p=0.560$
Sex	**$p=0.063$**	$p=0.303$	**$p=0.112$**	$p=0.450$	$p=0.505$	$p=0.506$
BMI	$p=0.758$	**$p=0.079$**	**$p=0.177$**	**$p=0.012$**	$p=0.526$	**$p=0.081$**
Season	**$p=0.085$**	$p=0.523$	$p=0.171$	$p=0.490$	$p=0.957$	$p=0.842$

Significant values are shown in bold.
VAS: visual analogue scale; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue – Multidimensional Questionnaire; ESR: erythrocyte sedimentation rate; 6MWT: six-minute walk test; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; BMI: body mass index.

Analyses of explanatory factors of fatigue recorded at the same time-point as the outcome

The result of univariate analyses to select which explanatory factors ($p < 0.25$) to include in the multivariable regression analysis full model are shown in Table III.

Multivariable analyses

The final models are shown in Table IV:

- *VAS fatigue:* VAS pain, Algometer, 6MWT, HADS-D, Sex and Season were included in the full multivariable model (see Table III). The final model included VAS pain, Algometer, HADS-D and Season. VAS pain ($p < 0.001$), Algometer ($p < 0.01$) and HADS-D ($p < 0.05$) were statistically significant.
- *BRAF-MDQ Total:* VAS pain, Algometer, 6MWT, HADS-D, and BMI were included in the full multivariable model (see Table III). The final model included VAS pain, Algometer, HADS-D, and BMI. Algometer ($p < 0.001$), HADS-D ($p < 0.001$), VAS pain ($p < 0.01$) and BMI ($p < 0.05$) were statistically significant.
- *BRAF-MDQ Physical:* VAS pain, Algometer, 6MWT, HADS-D, BMI, Sex and Season were included in the full multivariable model (see Table III). The final model included VAS pain, Algometer, HADS-D, BMI and Season. Algometer ($p < 0.001$), HADS-D ($p < 0.001$) and VAS pain ($p < 0.01$) were statistically significant.
- *BRAF-MDQ Living:* VAS pain, Algometer, 6MWT, HADS-D and BMI were included in the full multivariable model (see Table III). The final model included VAS pain, Algometer, HADS-D and BMI. Algometer ($p < 0.001$), HADS-D ($p < 0.001$), BMI ($p < 0.01$) and VAS pain ($p < 0.05$) were statistically significant.
- *BRAF-MDQ Cognitive:* VAS pain, Algometer, 6MWT and HADS-D were included in the full multivariable model (see Table III). The final model included VAS pain, Algometer and HADS-D. Algometer ($p < 0.001$) and HADS-D ($p < 0.001$) were statistically significant.
- *BRAF-MDQ Emotion:* VAS pain, Algometer, 6MWT, HADS-D and BMI were included in the full multivariable model (see Table III). The final model included Algometer, HADS-D and BMI. Algometer ($p < 0.001$) and HADS-D ($p < 0.001$) were statistically significant.

In the explanatory models the explained residual variances R^2_{resid} were 0.11–0.30, with the 2 highest values (0.30 and 0.25) for BRAF-MDQ Total and BRAF-MDQ Physical. The explained between-individual variances $R^2_{between\text{-}ind}$ were 0.46–0.64.

Analysis of predictors of fatigue with variables recorded at the time-point prior to the outcome (approximately 3 months)

The results from univariate analyses to select which predictors ($p < 0.25$) to include in the multivariable regression analysis full model are shown in Table V.

Multivariable analyses

The final models are shown in Table VI:

- *VAS fatigue:* Algometer, 6MWT, HADS-D, Sex and Season were included in the full multivariable model (see Table V). The final model included Algometer and HADS-D. Both Algometer ($p < 0.001$) and HADS-D ($p < 0.01$) were statistically significant.
- *BRAF-MDQ Total:* VAS pain, Algometer, HADS-D, BMI, Sex and Season were included in the full multivariable model (see Table V). The final model included VAS pain, Algometer, HADS-D, BMI and Sex. HADS-D ($p < 0.001$) and Algometer ($p < 0.01$) were statistically significant.
- *BRAF-MDQ Physical:* VAS pain, Algometer, 6MWT, HADS-D, Sex and Season were included in the full multivariable model (see Table V). The final model included Algometer, HADS-D and BMI. Algometer ($p < 0.001$) and HADS-D ($p < 0.01$) were statistically significant.
- *BRAF-MDQ Living:* VAS pain, Algometer, HADS-D, BMI, Sex and Season were included in the full multivariable model (see Table V). The final model included Algometer, HADS-D, BMI and Sex. HADS-D ($p < 0.001$), BMI ($p < 0.05$) and Sex ($p < 0.05$) were statistically significant.
- *BRAF-MDQ Cognitive:* VAS pain, Algometer, HADS-D, Age and Season were included in the full multivariable

Table IV. *Explanatory factors: multivariable analysis of explanatory factors of fatigue. The final models for each fatigue outcome are presented*

Explanatory factors	Estimate	95% CI
VAS Fatigue (n=65, 60, 58, 56)		
Intercept	33.594	20.321;46.868
VAS pain	0.451	0.337;0.565
Algometer	–0.0417	–0.072;–0.012
HADS-D	1.457	0.510;2.405
Season		
Winter (n=60)	6.68	0.996;12.366
Spring (n=58)	6.61	1.018;12.506
Summer (n=48)	6.60	0.307;12.885
Autumn (n=73)		
BRAF-MDQ Total score (n=65, 59, 58, 55)		
Intercept	15.290	4.071;26.509
VAS pain	0.0722	0.0262;0.118
Algometer	–0.0382	–0.0521;–0.0243
HADS-D	1.969	1.533;2.405
BMI	0.458	0.0546;0.861
BRAF-MDQ Physical subscale (n=65, 59, 58, 55)		
Intercept	9.889	5.305;14.472
VAS pain	0.0342	0.0150;0.0534
Algometer	–0.0145	–0.0202;–0.00872
HADS-D	0.513	0. 334;0.692
BMI	0.152	–0.0109;0.315
Season		
Winter (n=60)	0.930	0.00797;1.853
Spring (n=57)	0.721	–0.167;1.609
Summer (n=47)	0.711	–0.264;1.686
Autumn (n=73)		
BRAF-MDQ Living subscale (n=65, 60, 58, 55)		
Intercept	–0.455	–4.401;3.491
VAS pain	0.0177	0.00190;0.0334
Algometer	–0.0106	–0.0154;–0.00584
HADS-D	0.506	0. 356;0.655
BMI	0.238	0.0959;0.380
BRAF-MDQ Cognitive subscale (n=65, 60, 58, 55)		
Intercept	4.089	2.476;5.702
VAS pain	0.0139	–0.000248;0.0281
Algometer	–0.00724	–0.0111;–0.00336
HADS-D	0.549	0. 425;0.673
BRAF-MDQ Emotion subscale (n=65, 60, 58, 55)		
Intercept	0.733	–1.992;3.458
Algometer	–0.00624	–0.00954;–0.00293
HADS-D	0.435	0.329;0.540
BMI	0.095	–0.00427;0.194

VAS: visual analogue scale; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; HADS-D: Hospital Anxiety and Depression Scale–Depression subscale; BMI: body mass index.

Table VI. *Predictors: multivariable analyses of predictors of fatigue. The final models for each fatigue outcome are presented*

Predictors	Estimate	95% CI
VAS Fatigue (n=60, 56, 57)		
Intercept	63.820	49.636;78.004
Algometer	–0.0760	–0.114;–0.0380
HADS-D	1.869	0.596;3.141
BRAF-MDQ Total score (n=59, 56, 56)		
Intercept	11.014	–3.377;25.406
VAS pain	0.0450	–0.0261;0.116
Algometer	–0.0261	–0.0449;–0.00737
HADS-D	1.528	0.980;2.0758
BMI	0.412	–0.00976;0.834
Sex		
Women (n=6,135)	4.389	–1.265;10.0422
Men (n=636)		
BRAF-MDQ Physical (n=59, 56, 56)		
Intercept	11.376	6.211;16.540
Algometer	–0.0138	–0.0210;–0.00660
HADS-D	0.335	0.0981;0.571
BMI*	0.179	–0.00823;0.367
BRAF-MDQ Living (n=60, 56, 56)		
Intercept	–1.222	–6.130;3.686
Algometer	–0.00484	–0.0109;0.00117
HADS-D	0.430	0.249;0.611
BMI	0.153	0.00885;0.298
Sex		
Women (n=6136)	2.075	0.133;4.016
Men (n=636)		
BRAF-MDQ Cognitive (n=60, 56, 56)		
Intercept	4.846	3.249;6.443
Algometer	–0.00757	–0.0119;–0.00328
HADS-D	0.445	0.302;0.589
BRAF-MDQ Emotion (n=60, 56, 56)		
Intercept	0.673	–2.939;4.284
Algometer	–0.00547	–0.00983;–0.00110
HADS-D	0.273	0.141;0.406
BMI*	0.0734	–0.0346;0.181
Sex		
Women (n=6136)	1.038	–0.378;2.454
Men (n=636)		

*Did not enter the model according to univariate analysis, but was tested in the reduced model and was included.
VAS: visual analogue scale; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue – Multidimensional Questionnaire; HADS-D: Hospital Anxiety and Depression Scale – Depression subscale; BMI: body mass index.

Table V. *Predictions: univariate regression analyses to determine which predictors ($p < 0.25$) to include in the multivariable analysis full model*

		BRAF-MDQ				
Predictors	VAS Fatigue	Total	Physical	Living	Cognition	Emotion
ESR	p=0.593	p=0.721	p=0.682	p=0.257	p=0.993	p=0.507
VAS pain	p=0.273	**p=0.058**	**p=0.083**	**p=0.060**	**p=0.087**	**p=0.096**
Algometer	**p=0.000**	**p=0.001**	**p=0.001**	**p=0.016**	**p=0.002**	**p=0.002**
6MWT	**p=0.126**	p=0.483	p=0.237	p=0.488	p=0.407	p=0.848
HADS-D	**p=0.003**	**p=0.000**	**p=0.006**	**p=0.000**	**p=0.000**	**p=0.000**
Age	p=0.547	p=0.358	p=0.492	p=0.679	p=0.144	p=0.463
Sex	**p=0.078**	**p=0.114**	**p=0.131**	**p=0.104**	p=0.279	**p=0.159**
BMI	p=0.970	**p=0.243**	p=0.257	**p=0.124**	p=0.868	p=0.288
Season	**p=0.157**	**p=0.052**	**p=0.145**	**p=0.122**	**p=0.139**	p=0.265

Significant values are shown in bold.
VAS: visual analogue scale; BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; ESR: erythrocyte sedimentation rate; 6MWT: six-minute walk test; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; BMI: body mass index.

model (see Table V). The final model included Algometer and HADS-D. Both HADS-D ($p < 0.001$) and Algometer ($p < 0.01$) were statistically significant.

- *BRAF-MDQ Emotion:* VAS pain, Algometer, HADS-D and Sex were included in the full multivariable model (see Table V). The final model included Algometer, HADS-D, BMI and Sex. HADS-D ($p < 0.001$) and Algometer ($p < 0.05$) were statistically significant.

In the predictive models the explained residual variance R^2_{resid} ranged from –0.07 to –0.23 and the explained between-individual variances $R^2_{between\text{-}ind}$ were 0.44–0.69. The negative values of R^2_{resid} are explained by that the most negative values for R^2_{resid} were connected to the highest positive values on $R^2_{between\text{-}ind}$.

To investigate whether the results were influenced by baseline fatigue additional analyses of the predictive approach were performed with baseline fatigue inserted as a variable to predict fatigue. For each fatigue outcome measure the baseline fatigue ratings were added to the respective final model, i.e. the outcome VAS fatigue was controlled by baseline VAS fatigue in the final model. The results showed that HADS-D, Algometer and VAS pain remained as predictors of fatigue in 5 of 6 analyses. The exception was HADS-D for BRAF-MDQ Physical and Algometer for BRAF-MDQ Living. BMI and sex did not remain to be included in any of the models. Baseline fatigue significantly predicted later fatigue in all fatigue outcomes (see Table SI[1]).

At baseline there was a significant correlation ($p < 0.001$) between all fatigue variables ($r = 0.45–0.77$). The lowest correlation was seen between VAS fatigue and BRAF-MDQ Emotion ($r = 0.45$) and the highest correlation was seen between VAS fatigue and BRAF-MDQ Physical ($r = 0.77$).

DISCUSSION

This longitudinal study of fatigue, recorded at 4 time-points during 4 seasons in persons with RA, showed that pain threshold and depressive mood were the strongest factors explaining the fatigue, when measured at the same time-point as fatigue, and to predict fatigue 3 months later. Since this was found for general fatigue as well as for the other aspects of fatigue studied, pain threshold and depressive mood seem to relate to overall fatigue. Additional analysis found that fatigue at baseline was a predictor for later fatigue, and previous interviews in persons with RA indicate that fatigue itself uses up energy and thereby contributes to persistence of the fatigue (5). However, when controlling for baseline fatigue pain threshold and depressive mood remained important variables in predicting fatigue.

Depression has, in previous cross-sectional studies, been found to be one of the factors with strong association with fatigue in RA (6), but the results of studies analysing depression as a potential predictor of later fatigue are inconsistent. When comparing baseline fatigue with fatigue 1–2 years later, in one study depression was shown to be a statistically significant predictor of fatigue (23), while in 2 other studies depression failed to predict fatigue (24, 25). This implies that depressive mood is an important factor to take into account in the care of persons with RA.

Decreased pain thresholds have been found to be more common in persons with RA compared with a healthy control group, which may be due to both peripheral and central pain sensitization (26). In this study pain threshold was clearly related to all investigated aspects of fatigue in the multivariable regression models, both as an explanatory factor and as a predictor of fatigue.

Sleep problems are common in persons with RA and have been found to be associated with fatigue in these subjects (27). Previous studies show that poor sleep quality is associated with increased pain sensitivity (9, 10) as well as with depression (27), implying that the relationship between decreased pain thresholds, depression and fatigue may be mediated by poor sleep. However, due to cross-sectional study designs in the previous studies, the causal relationships between sleep quality, pain thresholds, depressive mood and fatigue are unclear and investigations with a longitudinal approach are necessary.

Interestingly, we found the ratings of pain on VAS to be an explanatory factor of fatigue when recorded at the same time-point, but not to predict fatigue 3 months later. This is in line with previous results concluding that fatigue and pain have an association, but not that one precedes or causes the other (28). In this study we found VAS pain to strongly explain the physical aspects of fatigue (i.e. BRAF-MDQ Physical and Living) suggesting that pain intensity may influence the energy and the ability to cope, physically and socially. Previous studies show a weak association between pain threshold and VAS pain in persons with rheumatic diseases and chronic pain (29, 30), while stronger association has been observed between pain threshold and depression (30), both of which relate to the central nervous system. This highlights the multifaceted nature of pain in RA, which can be influenced by peripheral and central pain sensitization beyond inflammation (10, 26). Our results confirm this complex relationship between pain threshold, depressive mood and fatigue.

Physical activity has been found to be inversely associated with fatigue (31, 32) and the results of exercise interventions in persons with RA show positive effects on fatigue (33) as well as on pain (33, 34), depression (33) and sleep quality (35). A large international study in persons with RA found significantly higher fatigue levels among physically inactive persons compared with those who were physically active (36). This implies that physical activity and exercise interventions may be a useful tool in planning interventions to diminish fatigue. Furthermore, physical activity is assumed to result in positive effects on pain and depressive mood, factors found to be of importance for fatigue in this study.

Physical capacity measured with 6MWT showed an ambiguous association with fatigue. In the univariate analysis

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2090

when physical capacity was recorded at the same time-point as fatigue, a significant association was seen between 6MWT and all fatigue outcomes. However, in the multiple regression models, when covariability was accounted for, 6MWT did not remain significant. Physical capacity measured with 6MWT was neither found to be a predictor of fatigue 3 months later in the univariate or multivariable analysis. According to these results there does not seem to be a causal relationship between physical capacity measured with 6MWT and the variation in fatigue. One possible explanation of the association in the univariate analyses, when recorded at same time-point as fatigue, may be that fatigue influences the performance on the 6MWT and not the other way around (32).

BMI appears to be of potential importance when studying fatigue, given that higher BMI was associated with higher ratings of fatigue. A significant impact of BMI was seen in BRAF-MDQ Living, reflecting the impact of fatigue on the ability to perform activities in everyday life. In RA the inflammatory process has been found to lead to a degradation of lean tissue, especially muscle mass. In combination with inactive lifestyle persons with RA are predisposed to reduced muscle mass and accumulation of body fat, leading to increased adiposity despite stable weight (37, 38). Therefore, BMI is questioned as a reliable measure of overweight and obesity among persons with RA; therefore future studies of the association of body composition and fatigue in RA are of interest.

Seasonal variations in symptoms are often described by persons with RA, but clinical studies have so far failed to show such association (39). In this study season was, in the explanatory multivariable model, found to be a factor of potential importance for general fatigue and the physical aspects of fatigue.

In this study no associations were found between ESR and fatigue. This is in line with the results found in 5 of 6 studies, which showed no association between ESR or CRP and fatigue (6). However, other inflammatory biomarkers might be associated with fatigue (40), which warrants further investigation.

Age or sex did not have an impact on fatigue in our study. However, the analysis was limited to the age criteria of 20–65 years, with a low number of participants in the younger ages and although the distribution of women and men was in concordance with a general RA population, the number of men in this study was limited ($n = 17$). Previous studies have also failed to show a relationship between fatigue and age, and the relationship between sex and fatigue are showing inconsistent associations (6).

In the current study we applied a multidimensional instrument to rate fatigue. Other researchers suggest that fatigue can be assessed as a unidimensional construct (41). In addition, our analyses show that the different aspects of fatigue correlate with each other and with the one-dimensional VAS. However, it appears that some aspects of fatigue may be easier to treat than others, as in a recent treatment study we found most impact on physical fatigue from an intervention comprising physical activity (42).

The variables in the final models were able to explain a considerable ratio of the variation in fatigue, both at the individual level and at the group level. In the predictive models the result was inconsistent. The variables in the final models seemed to mainly handle the between-individual, rather than the residual variation in fatigue. This indicates that the models were able to predict the level of fatigue rather than change in fatigue. The goodness-of-fit measure used here is R^2. It has the useful property of providing an absolute value for the goodness-of-fit of a model, and the amount of variance explained can be of biological interest. Information criteria, e.g. Akaike Information Criteria, cannot provide this information. One problem, however, of R^2 for mixed-effects models is that it can be defined in several ways. Despite the problems of the R^2 chosen here (e.g. decreased or negative R^2 values in larger models), common for several definitions of R^2 for mixed-effects models, the choice here is based on their relatively intuitive interpretation and simplicity.

Strengths and weaknesses

Strengths of this study were the longitudinal design and the use of multivariable analysis method, enabling us to draw conclusions about possible explanatory factors and predictors of fatigue.

Limitations of this study were the use of parametric methods with ordinal data which limits the possibility to draw conclusions about the magnitude of the estimates. Also, one should be cautious in generalizing the results due to small sample size. In this study, all results of all models are presented, but only the main patterns in the results are interpreted.

Conclusion

In conclusion, pain threshold and depressive mood appear to be important factors for general as well as physical, cognitive and emotional aspects of fatigue in persons with rheumatoid arthritis. Pain intensity appears to be an important factor to discuss when a patient reports physical fatigue.

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