FATIGUE IN RHEUMATOID ARTHRITIS PATIENTS WITH LOW DISEASE ACTIVITY

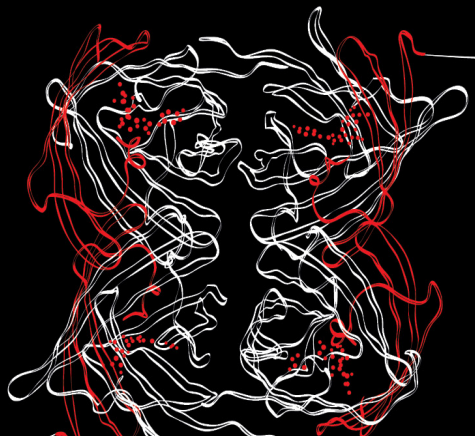
A thesis submitted in fulfilment of the requirements for the degree of Master of Science in Health Psychology

Author:
L.I.M. Lenferink

Suporvisors:
C. Bode, PhD
S. Nikolaus, PhD
H. E. Vonkeman, MD, PhD (Medisch Spectrum Twente)

Faculty:
Behavioral Science

Department:
Psychology, Health & Technology



UNIVERSITY OF TWENTE.

Enschede, October 2013

Dankwoord

Met trots sluit ik met deze masterthese mijn studieperiode aan de Universiteit van Twente af. Ik heb de gehele studieperiode als ontzettend leerzaam ervaren en naarmate de studie vorderde, kreeg ik steeds meer interesse in het uitvoeren van onderzoek. Christina, jij bent diegene geweest die mij enthousiasmeerde om de master gezondheidspsychologie te volgen en gaf mij de kans dit onderzoek uit te voeren. Jij hebt mij gestimuleerd om het onderste uit de kan te halen. Graag wil ik je bedanken voor jouw kritische blik, ondersteund commentaar en enthousiasme. Samenwerken met jou is een feest! Stephy, ik vind het een eer dat jij de rol als tweede begeleidster wilde vervullen. Jouw expertise op het gebied van vermoeidheid bij patiënten met reumatoïde artritis, heeft enorm bijgedragen aan de totstandkoming van dit werk. Jij hebt mij sturing gegeven waar nodig en altijd met aandacht de tussentijdse versies van mijn these gelezen en becommentarieerd, waarvoor hartelijk dank. Harald, bedankt dat jij als externe begeleider vanuit medisch perspectief mijn these wilde begeleiden. Jouw directe manier van communiceren vond ik verhelderend. Jouw kritische blik heeft mijn werk aangescherpt. Alle patiënten wil ik bedanken voor deelname. Zonder jullie was het onmogelijk om dit onderzoek uit te voeren. Peter, jou wil ik bedanken voor de tijd die je vrijmaakte om mij te instrueren over SPSS-toepassingen. Jo, thank you for reading my thesis. Ariena, bedankt voor jouw nauwkeurige nakijkwerk, m.b.t. het taalgebruik in mijn these. Marijke, bedankt voor het reviewen van de conceptversie van mijn these. Jouw aanpassingen waren zeer welkom.

Pap en mam, ik ben trots dat ik jullie dochter ben. Jullie hebben mij geleerd wat hard werken en doorzetten is. Bedankt voor jullie steun.

Charell, een betere vriendin kan ik mij niet wensen. Jij bent er altijd geweest wanneer ik een luisterend oor of juist afleiding nodig had. Jij weet als geen ander hoeveel dit afstudeerproject voor mij betekent. Bedankt voor je onvoorwaardelijke steun en vertrouwen. Lieve vriendinnetjes Minou, Marieke, Geke en Ottilie, jullie bedankt voor de fijne, ontspannende momenten tijdens mijn afstudeerperiode.

Klaas-Jelmer, wat ben ik blij dat jij in mijn leven bent. Jij bent de constante factor die mij op kan beuren, bedaren en bevestigen. Wetende dat jij mij altijd steunt, maakt mij een gelukkig mens.

Abstract

Objectives Fatigue is reported to be one of the most common symptoms among people with rheumatoid arthritis (RA). Although rheumatologists are highly effective in controlling disease activity, patients still experience fatigue. The primary aim of this study was to analyse the relation between disease activity and multidimensional fatigue by using a novel multidimensional fatigue questionnaire (BRAF-MDQ) in RA patients with low disease activity. First the prevalence of clinically relevant fatigue was examined. As the Dutch translation of the BRAF-MDQ had not been validated yet, the second aim was to evaluate the BRAF-MDQ psychometrically. Thirdly, the possible differences in scores on the fatigue dimensions between patients with non-clinically relevant fatigue, clinically relevant fatigue and clinically severe fatigue were explored. The final aim was to determine how multidimensional fatigue is related to disease activity and health-related quality of life (HRQoL).

Methods The data of 199 RA patients (69 % women, mean age 59 years, mean DAS-28 score 1.99) were selected from a multi-centre randomized clinical trial. Firstly, the prevalence of fatigue was examined, using a numeric rating scale of fatigue. Spearman Rho correlations were used to determine how multidimensional fatigue was related to disease activity and HRQoL, using the DAS-28 score and the SF-36 respectively. The dimensional structure, item internal consistency, item discriminant validity, distinctiveness and reliability, external construct validity and possible floor- and ceiling effects were examined to psychometrically evaluate the BRAF-MDQ. Mann-Whitney U-tests were utilized to explore whether the scores on the dimensions significantly differed between patients with different severities of fatigue.

Results Clinically relevant fatigue was highly prevalent (73 %) in RA patients with low disease activity. The four-dimensional structure of the BRAF-MDQ was broadly confirmed, however major floor effects were detected for three dimensions. The scores on the dimensions differed significantly between patients with different severities of fatigue. The correlation coefficients between disease activity and dimensions of fatigue ranged from .05 to .09 and significant moderate to strong relations were shown for HRQoL.

Discussion The findings indicate that even though RA inflammation is clinically under control, the majority of the patients still reported clinically relevant fatigue. Moreover, fatigue does not necessarily interfere with patients' daily, social, emotional and cognitive life. Although the four-dimensional structure of the BRAF-MDQ is broadly confirmed, the major floor effects point to possibilities for improvement of fatigue measurement by, for example, computer adaptive testing

Table of Contents

Introduction

Fatigue is, alongside pain, the most disturbing symptom for patients with rheumatoid arthritis (RA) (Tack, 1990; Wolfe, Hawley, & Wilson, 1996). Fatigue often has a serious negative impact on quality of life and daily functioning and it is experienced as overwhelming, uncontrollable and not restored by sleep (Dupond, 2011; Hewlett et al., 2005; Staud, 2012). For rheumatologists, fatigue is a challenging phenomenon to deal with. Firstly, fatigue is a nonspecific and subjective symptom, as it is prevalent in various conditions and patients refer to it in various ways (Dupond, 2011; Hewlett, Hehir, & Kirwan, 2007). Secondly, no consensus has been reached among health specialists about the exact definition and meaning of fatigue (Dupond, 2011). It is, however, accepted among clinicians and researchers that fatigue in RA is different from normal tiredness (Dupond, 2011; Hewlett, et al., 2007; Oncu, Basoglu, & Kuran, 2013). Qualitative studies of the experience of fatigue in RA, which incorporated patient-perspectives, support this assumption and suggest that fatigue has multiple components that impact every aspect of life, including physical, social, cognitive and emotional activities (Feldthusen, Björk, Forsblad-d'Elia, & Mannerkorpi, 2012; Hewlett, et al., 2005; Repping-Wuts, Uitterhoeve, van Riel, & van Achterberg, 2008).

Although the treatment of RA has improved over the last decades and clinicians are highly effective in controlling disease activity (Singh et al., 2009), up to 90 % of RA patients still suffer from clinically relevant fatigue (Belza, Henke, Yelin, Epstein, & Gilliss, 1993; Kalyoncu, Dougados, Daurès, & Gossec, 2009; Wolfe, et al., 1996; Yacoub Ibn et al., 2012). This has lead to a new discussion about the pathogenesis of fatigue. The traditional premise that disease activity plays a dominant role in the occurrence and maintenance of fatigue must be called into question (Repping-Wuts, Van Riel, & Van Achterberg, 2009). A recent systematic review showed conflicting results regarding the relation between fatigue and disease activity (Nikolaus, Bode, Taal, & van de Laar, 2013a). Some studies found that disease activity was significantly related to fatigue (Dhir, Lawrence, Aggarwal, & Misra, 2009; Huyser et al., 1998; Thyberg, Dahlström, & Thyberg, 2009), but other studies did not find an association at all (Contreras-Yanez, Cabiedes, Villa, Rull-Gabayet, & Pascual-Ramos, 2010; Pollard, Choy, Gonzalez, Khoshaba, & Scott, 2006; Repping-Wuts, Fransen, Van Achterberg, Bleijenberg, & Van Riel, 2007; Stebbings, Herbison, Doyle, Treharne, & Highton, 2010; Wolfe, et al., 1996). More consistent were the results of the relation between fatigue and pain, physical functioning, sleep disturbance, depression and health-related quality of life (HRQoL) (Nikolaus, et al., 2013a). Hewlett et al. (2011a) proposed a

hypothetical model of the determinants of fatigue that suggests interactions between disease-related, personal, cognitive and behavioural factors. However, up to this date the understanding of the origin of fatigue in RA is incomplete.

Since patients suggest that fatigue is multi-faceted (Nicklin, Cramp, Kirwan, Urban, & Hewlett, 2010b; Repping-Wuts, et al., 2008), it would be advantageous to actually measure all these facets. However, the current most frequently used fatigue measure is the visual analog scale (VAS), which is a single-item measure (Hewlett, et al., 2007; Hewlett, Dures, & Almeida, 2011b). The respondent is instructed to rate their severity of fatigue on a 10 cm scale. The response options are not standardized which limits the comparisons between studies (Hewlett, et al., 2011b). Therefore the Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scales (BRAF NRS) for severity, coping and effect of fatigue were developed, which showed strong construct and criterion validity (Hewlett, et al., 2011b). Although these single-item measures may be a useful and quick tool, they do not give a full understanding of the complete fatigue experience.

Several multi-item and multidimensional fatigue measures are available, but they have psychometric shortcomings. They either produce a single global fatigue score, they do not capture all fatigue components, they are not validated in a RA population, or items are interpretable in more than one way (Hewlett, et al., 2011b; Nicklin, 2009). Hence Nicklin et al. (2010a, 2010b) developed the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ), a multidimensional fatigue measure for specific use in RA studies. The strength of the BRAF-MDQ lies in the development from the patient-perspective. The 20-item questionnaire contains four distinct dimensions of fatigue labelled as physical, living with, emotional and cognitive fatigue which showed good reliability, internal consistency, criterion validity, construct validity and sensitivity to change (Dures et al., 2013; Nicklin et al., 2010a). The physical dimension corresponded mostly with the existing measures of fatigue and appeared to measure severity of fatigue. Living with fatigue represented the impact of fatigue on daily life and social life. Emotional fatigue displayed the way fatigue affected feelings. The fourth and final dimension, cognitive fatigue, reflected the way fatigue influenced information processes and mental performances (Nicklin, et al., 2010a)

Although the first evaluations of the English BRAF-MDQ indicated good psychometric qualities (Dures, et al., 2013; Nicklin, et al., 2010a), this instrument has not yet been widely used (Hewlett, et al., 2011b; Nicklin, et al., 2010a). The BRAF-MDQ has been translated into

34 languages, including a Dutch version, using proper methods (see Dures et al., 2013 for details). However, the Dutch translation has not been validated yet.

The primary aim of this study was to analyse the relation between disease activity and multidimensional fatigue in RA patients with predominantly low disease activity, by using the Dutch version of the BRAF-MDQ, which has never been studied before. In order to do so, firstly the prevalence of clinically relevant levels of fatigue was examined in RA patients with predominantly low disease activity to see to what extend fatigue is present in patients whose RA is clinically under control.

As the Dutch translation of the BRAF-MDQ had not been validated yet, the second aim of this study was to evaluate the psychometric properties of the BRAF-MDQ. Age, disease duration and variables of HRQoL, including pain, physical functioning and psychosocial variables were included for assessing the external construct validity of the BRAF-MDQ. Hypotheses regarding the strength of these relations were based on previous research (see appendix II table 1 for an overview of the hypotheses). Based on a recent systematic review of Nikolaus et al. (2013), it was hypothesized that the dimensions of fatigue would not or only weakly correlate ($r < .30$ or $> -.30$) with age and disease duration. In contrast, at least moderate correlations were expected between variables of HRQoL and dimensions of fatigue, as previous correlational studies in RA showed overall moderate ($r \geq -.30 < -.50$) to strong relations ($r > -.50$) between variables of HRQoL and fatigue (Prevoo et al., 1995; Rupp, Boshuizen, Jacobi, Dinant, & Van Den Bos, 2004; van Hoogmoed, Fransen, Bleijenberg, & van Riel, 2010; Yacoub Ibn, et al., 2012). Furthermore, a strong relation ($r > -.50$) was expected between vitality as a subscale of HRQoL and dimensions of fatigue, because the vitality subscale is often used as fatigue measure (Hewlett, et al., 2011b).

The third aim of this study was to analyse possible (significant) differences in frequency and distribution of the scores on the dimensions between patients with non-clinically relevant, clinically relevant and clinically severe fatigue. This was an explorative approach that intended to further our understanding of the concept of multidimensional fatigue.

Finally, the content of the relation between dimensions of fatigue on the one hand and disease activity and variables of HRQoL on the other hand was analysed. There were no expectations about the strength of the relation between disease activity and dimensions of fatigue due to conflicting results in previous research (Nikolaus, et al., 2013a). The hypotheses about the strength of the relations between variables of HRQoL and dimensions of fatigue were previously assessed in order to determine the external construct validity of the BRAF-MDQ (see hypotheses table appendix II, table 1), but this time the content of these

relations was analysed. The developers of the BRAF-MDQ argued for separate fatigue dimensions and they found that the dimensions correlated differently with pain, daily functioning, mood and anxiety (Nicklin, et al., 2010a). It was therefore plausible to expect that the relations with variables of HRQoL also differed between the separate dimensions of fatigue. It was expected that the dimensions of fatigue would correlated stronger with variables that showed the most theoretical conformity: thus, the living with dimension with the physical and social orientated variables of HRQoL, and the emotional dimension with the emotional orientated variables of HRQoL (see appendix II table 1). The cognitive dimension had a deviating character compared to the other dimensions and it was expected that this dimension had the least strong correlation with the variables of HRQoL. Due to the general character of the physical dimension no specific expectations were formulated for this dimension (Nicklin, et al., 2010a).

The following research questions were answered within this study:

1 *What is the prevalence of clinically relevant levels of fatigue in RA patients with predominantly low disease activity?*

2 *To what extend is the Dutch translation of the BRAF-MDQ a psychometrically sound multidimensional fatigue measure in RA patients with predominantly low disease activity*?

3 *To what extend do the frequency and distribution of the scores on the dimensions of fatigue differ between patients with non-clinically relevant fatigue, clinically relevant fatigue and clinically severe fatigue?*

4 *To what extend are the dimensions of fatigue related to disease activity and variables of HRQoL in RA patients with predominantly low disease activity?*

Methods

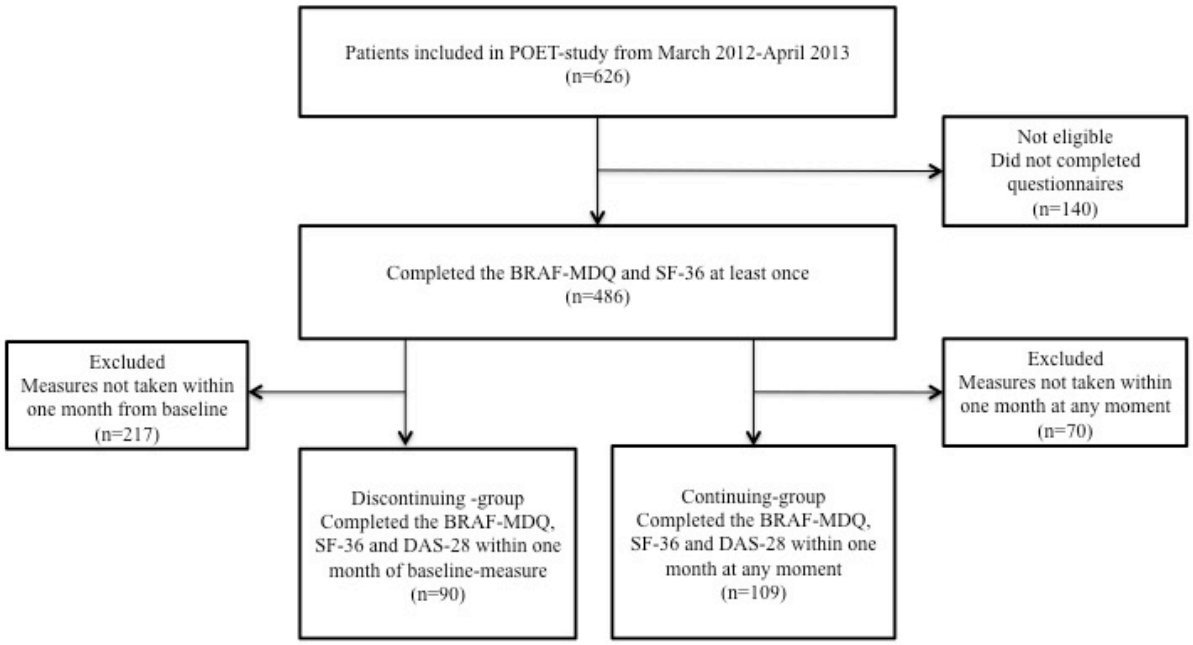
Procedure

The present cross-sectional study was embedded in the on-going multicentre longitudinal study named 'Potential optimalisation of (Expediency) and Effectiveness of TNF-blockers' (POET) (ZonMw project number: 152041002, trial register number: 3112). The POET-study is a cooperative initiative of different Dutch rheumatology clinics, which aims to determine whether it is possible to discontinue anti-TNF treatment in RA patients with stable low disease activity. Inclusion criteria for the POET-study were having rheumatoid arthritis according to the 1987 revised American College of Rheumatology classification criteria for RA (Arnett et al., 1988), using anti-TNF treatment ≥ 1 year, low disease activity during the last 6 months (DAS28 score of ≤ 3.2) and the presence of written informed consent. After inclusion, the patient was randomly assigned to the 'discontinuing anti-TNF therapy-group' or to the 'continuing anti-TNF therapy-group'. Additional inclusion criteria for the current study were being included in the POET-study from March 2012 till April 2013 and having completed the BRAF-MDQ and the SF-36 at least once on the same day and the DAS-28 within one month of this date. For the patients of the 'discontinuing anti-TNF therapy-group' only baseline-measures, which were taken within one month, were included. A specific time frame of one month for all data to be collected was desirable to minimize the risk of possible fluctuations, which would bias the results. As there is no full understanding of the fluctuating nature of fatigue and disease activity in RA, we followed the example of a previous study (Van Dartel et al., 2013) and chose to select data within a time frame of one month. Data were collected through clinical assessments and self-administered questionnaires. Ethical approval of the POET-study protocol was obtained from the local medical ethics committees.

Patients

From March 2012 to April 2013 a total of 676 patients were included in the POET-study, of which 486 patients at least once completed the BRAF-MDQ and the SF-36 on the same day. Ninety patients of the 'discontinuing anti-TNF therapy-group' completed the BRAF-MDQ, SF-36 and DAS-28 within one month from baseline and 109 patients of the 'continuing anti-TNF therapy-group' completed these measures within one month from baseline or at a follow-up moment. Consequently, 199 patients were included in this study (see figure 1 for flowchart).

Figure 1. Inclusion procedure of patients



The majority of the sample was female (69 %) and mean (SD and range) age in 2013 was 59.07 years (11.24 and 25-83), DAS-28 score was 1.99 (0.84 and 0.49–6.12), and disease duration at 18th of September 2013 was 12.11 years (8.93 and 2-51). In terms of severity of RA, the presence of erosive in the sample at baseline was 56 % and positive rheumatoid factor 64 %. See table 1 for the demographic data and disease characteristics. No significant differences were found for these demographic and disease-related variables between the patients who were included and excluded, except for erosives ($\chi^2 = 5.80$, df=1, p = .02)

Table 1. Demographic data and disease characteristics (n=199)

	Frequency (%)	Mean (SD)
Demographics		
Male	62 (31)	
Female	137 (69)	
Age in years in 2013		59.07 (11.24)
Missing data	1 (1)	
<40 years	9 (5)	
40-59 years	86 (43)	
≥ 60 years	103 (52)	
Missing data	1 (1)	
Disease characteristics		
DAS-28 score		1.99 (0.84)
Disease duration in years		12.11 (8.93)
Erosive		
Yes	112 (56)	
No	87 (44)	
Rheumatoid factor positivity		
Positive	128 (64)	
Weak/positive	10 (5)	
Negative	61 (31)	

Measures used

Fatigue. The BRAF-MDQ is supposed to cover four distinct dimensions of fatigue: physical fatigue (4 items) (e.g. How many days did you experience fatigue during the past week?), living with fatigue (7 items) (e.g. Has fatigue made it difficult to bathe or shower?), cognitive fatigue (5 items) (e.g. Have you forgotten things because of fatigue?) and emotional fatigue (4 items) (e.g. Have you felt down or depressed because of fatigue?). Response options ranged from 'not at all', 'a little', 'quite a bit' to 'very much' on a scale of 0-3, except for the first 3 items, which are numerical or categorical, with higher scores indicating higher levels of fatigue (item 1 scored 0-10, 2 scored 0-7 and 3 scored 0-2). All items had a 1-week recall-period. Fatigue scores per subscale are obtained by summing the scores on these scales. Physical fatigue score ranged from 0-22, living with fatigue ranged from 0-21, cognitive

fatigue ranged from 0-15, and emotional fatigue ranged from 0-12 (see appendix I for the BRAF-MDQ).

The scores on a BRAF NRS severity of fatigue were used to answer the first and third research question. The BRAF NRS severity of fatigue is part of the physical dimension of the BRAF-MDQ, but is also suitable for independent use to assess the severity of fatigue. The patient is instructed to circle the number that best reflects the average level of fatigue during the past 7 days, with 0 "no fatigue" and 10 "totally exhausted" (Hewlett, et al., 2011b).

Disease activity score. The 28-joint disease activity score (DAS-28) was assessed by a rheumatologist or a specialized rheumatology nurse in order to determine the activity of RA. This is a validated measure and it is extensively used in clinical trials and clinical practice (Prevoo, et al., 1995). The DAS-28 score provides a score by counting the tender and swollen joints, assessing the Erythrocyte Sedimentation Rate (ESR-rate) in mm/hour and assessing patients' global health rating on a 100 mm well-being or disease activity visual analogue scale (Fuchs, 1993). Total scores range between 0-10, with higher scores indicating higher disease activity. The following formula was used for calculating this score; DAS28 = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * VAS.

Health-related quality of life. HRQoL was assessed with the Dutch version of the 36-item short-form health survey (SF-36), which is a validated, self-administrated and internationally used health status questionnaire for assessing HRQoL (ten Klooster et al., 2013). The patient is instructed to indicate to what extend the statement applies to him/her. The 8 subscales include: physical functioning ($\alpha = .92$, 10 items, e.g. Walking more than a mile), role-physical ($\alpha = .95$, 4 items, e.g. Accomplished less than you would like) bodily pain ($\alpha = .84$, 2 items, e.g. How much bodily pain have you had?), general health ($\alpha = .82$, 5 items, e.g. My health is excellent), vitality ($\alpha = .77$, 4 items, e.g. Did you feel tired?), social functioning ($\alpha = .82$, 2 items, e.g. Emotional problems interfered with your normal social activities with family, friends, neighbours, or group?) role-emotional ($\alpha = .92$, 3 items, e.g. Didn't do work or other activities as carefully as usual) and mental health ($\alpha = .88$, 5 items, e.g. Have you been a happy person?). All items had a 4-week recall-period. The response options differed from dichotomous to a 5-point Likert scale. Standardized scores from 0-100 were computed for each subscale, with lower scores indicating poorer HRQoL.

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 20 for Macintosh (IBM, 2011). A one-sided significance level of $\alpha = 0.05$ was chosen for all

analyses, because the hypotheses were directional. Except for the correlational analysis with age, disease duration and disease activity a two-sided significance level was chosen. The frequency, percentages, means and SD were calculated for the demographic variables. Because fatigue data were not normally distributed, Spearman's Rho correlation was used for all variables.

In order to answer the first research question, data of the BRAF NRS severity of fatigue and the DAS-28 were utilised to examine the prevalence of clinically relevant levels of fatigue. Data of the BRAF NRS severity of fatigue instead of the BRAF-MDQ were used, because cut-off scores for the BRAF-MDQ are not yet available or reducible. The cut-off scores for the BRAF NRS severity of fatigue were defined according to previously used cut-off scores of the VAS fatigue (Nicklin, et al., 2010a; Pollard, et al., 2006). Previous research showed strong correlation between the BRAF NRS severity of fatigue and VAS fatigue (r = .78) and no significant differences in means (Nicklin, et al., 2010a). Hence, the following cut-off scores were used: non-clinically relevant fatigue (< 2), clinically relevant fatigue (≥ 2 < 5) and clinically severe fatigue (≥ 5). The percentages of frequency of scores ≥ 2 were used as indicator of clinically relevant levels of fatigue. Validated cut-off scores of the DAS-28 were used as an indicator for low disease activity (≤ 3.2), moderate disease activity (> 3.2 ≤ 5.1) and high disease activity (> 5.1) (Felson et al., 2011; Gestel v. AM, 1998; Yacoub Ibn, et al., 2012).

In order to answer the second research question, the distribution of the fatigue data was observed first. Mean and SD for each item as well as for the dimensions were calculated. Different techniques were used to evaluate the psychometric quality of the BRAF-MDQ. Firstly, the dimensional structure was explored by a principal component analysis (PCA) with direct oblimin rotation. Scree plot with Cattell's cut-off point, the Kaiser's criterion with eigenvalues over 1 and theoretical support were used for extracting the number of factors (Field, 2009). Secondly, item internal consistency was considered acceptable when the item correlated ≥ .30 with the total score on the corresponding dimension, with exclusion of that particular item (Field, 2009). Thirdly, the correlation of the items with the corresponding dimension should be higher than the correlation with the non-corresponding dimension, in order to speak of item-discriminant validity. Fourthly, to determine the distinctiveness of the dimensions correlation analyses were performed between the dimensions. Strong correlations (> 0.70) between dimensions were labelled as undesirable as this could suggest that these dimensions are interchangeable. Fifthly, a Guttman's Lambda 2 ≥ 0.7 was used as a criterion for good reliability of the dimensions of the BRAF-MDQ, as this is a more precise estimator

of the reliability than Cronbach's alpha (Sijtsma, 2009). Sixthly, external construct validity was examined by analysing the divergent and convergent validity. The following criteria for strength of correlations were used: correlations of ≥ .50 or ≤ -.50 were considered as strong, ≥ -.30 < -.50 or ≥ .30 < .50 as moderate and < .30 or < -.30 as weak (Cohen, 1988). Finally, if more than 15 % of the patients responded with the lowest or highest sumscore on the dimensions, it was rated negatively for floor or ceiling effects (Terwee et al., 2007).

In order to answer the third research question the frequency and distribution of the scores on the fatigue dimensions of the total sample were visualised in a graphic first. Then the frequency and distribution of the scores on the fatigue dimensions of patients with different severities of fatigue, using cut-off scores of the BRAF NRS severity of fatigue, were visualised in a graphic and compared to each other. Possible significant differences in the scores on the dimensions of fatigue between patients with non-clinically relevant, clinically relevant and clinically severe fatigue were analysed with the Kruskal-Wallis test and post hoc Mann-Whitney U-tests with Bonferonni-correction (p = .050/3).

In order to answer the final research question, the correlation between disease activity and the dimensions of fatigue was computed. The correlations with the variables of HRQoL had already been computed to assess the external construct validity of the BRAF-MDQ, but this time the content of these relations between variables of HRQoL and dimensions of fatigue was analysed.

Results

Prevalence of fatigue

Clinically relevant fatigue (BRAF NRS score of ≥ 2 < 5) was present in 38 % of the patients. Clinically severe fatigue (BRAF NRS score of ≥ 5) was present in 35 % of the patients. Almost the total sample (96 %) had low disease activity. To answer the first research question, these results show that clinically relevant levels of fatigue are highly prevalent (38 + 35 = 73 %) in patients with predominantly low disease activity. See table 2 for an overview of the prevalence of severity of fatigue per category of disease activity.

Table 2. Frequency and percentages of severity of fatigue and disease activity

	Severity of fatigue			
Disease activity	Clinically severe fatigue *n* (%)	Clinically relevant fatigue *n* (%)	Non-clinically relevant fatigue *n* (%)	Total *n* (%)
Low disease activity	63 (33)	75 (39)	53 (28)	191 (96)
Moderate disease activity	6 (86)	1 (14)	0 (0)	7 (4)
High disease activity	0 (0)	0 (0)	1 (100)	1 (1)
Total	69 (35)	76 (38)	54 (27)	199 (100)

Note. Categories of DAS-28 scores (range 0-10): low disease activity ≤ 3.2; moderate disease activity > 3.2 ≤ 5.1; high disease activity > 5.1. Categories of BRAF NRS severity of fatigue scores (range 0-10): clinically severe fatigue (≥ 5); clinically relevant fatigue (≥ 2 < 5); non-clinically relevant fatigue (< 2).

Evaluation of the psychometric properties of the BRAF-MDQ

Distribution of the data. The frequency of the responses to each item of the BRAF-MDQ was observed and is shown in appendix II table 2. The mean score ± SD for each dimension was 8.51 ± 5.67 for physical fatigue (range 0-22), 3.31 ± 3.95 for living with fatigue (range 0-21), 1.88 ± 2.39 for cognitive fatigue (range 0-15) and 1.22 ± 1.80 for emotional fatigue (range 0-12) (see appendix II table 3)

Dimensional structure. The first step of the psychometric evaluation of the BRAF-MDQ was to explore the dimensional structure. A principal component analysis (PCA) with oblique rotation (direct oblimin) revealed four components with eigenvalues of ≥ 1 that in total explained 73.33 % of the variance. The scree plot was interpretable in different ways, due to

inflexions at the second and the sixth component. Given the theoretical conformity, Kaiser's criterion with eigenvalues of ≥ 1 instead of the scree plot was decisive and lead to the extraction of four components. The component loadings after rotation are shown in table 3.

Component 1 seemed to represent living with fatigue (explained variance of 54.19), component 2 physical fatigue (explained variance of 7.49), component 3 emotional fatigue (explained variance of 6.36), and component 4 cognitive fatigue (explained variance of 5.29). All items loaded ≥ 0.57 with their corresponding dimension and ≤ .34 with the non-corresponding dimensions, except for item 7 and 8 of the living with dimension, item 12 of the cognitive dimension and item 17 of the emotional dimension, which loaded higher on a non-corresponding dimension than on their corresponding dimension. Other anomalies were the component loading of item 9 and item 11 of the living with dimension. These items loaded the highest on their corresponding dimension, but also relatively high on a non-corresponding dimension (see the bold displayed component loadings in table 3). The overall fit of the results of the PCA and the theoretical structure of the BRAF-MDQ was satisfactory.

Table 3. Component loadings for the BRAF-MDQ (n = 199)

		Components			
Item number	**Dimensions of fatigue, items**	**1**	**2**	**3**	**4**
	Physical				
1	BRAF NRS severity of fatigue		-0.74		
2	How many days?		-0.84		
3	How long on average has each episode of fatigue lasted?		-0.85		
4	Have you lacked physical energy because of fatigue?		-0.77		
	Living with				
5	Has fatigue made it difficult to bathe or shower?	0.80			
6	Has fatigue made it difficult to dress yourself?	0.85			
7	Has fatigue made it difficult to do your work or other daily activities?	**0.32**	**-0.60**		
8	Have you avoided making plans because of fatigue?	**0.39**	**-0.41**		
9	Has fatigue affected your social life?	**0.45**	**-0.34**		

10	Have you cancelled plans because of fatigue?	0.62		0.34	
11	Have you refused invitations because of fatigue?	**0.56**		**0.42**	
	Cognitive				
12	Have you lacked mental energy because of fatigue?			**0.31**	**0.30**
13	Have you forgotten things because of fatigue?				0.79
14	Has fatigue made it difficult to think clearly?				0.65
15	Has fatigue made it difficult to concentrate?				0.66
16	Have you made mistakes because of fatigue?				0.83
	Emotional				
17	Have you felt you have less control because of fatigue?				**0.54**
18	Have you felt embarrassed because of fatigue?	0.33		0.57	
19	Has being fatigued upset you?			0.79	
20	Have you felt down or depressed because of fatigue?			0.80	
Explained variance (%)		54.19	7.49	6.36	5.29

Note. Component loadings of < 0.30 were not displayed. Bold displayed loadings are described in the text in more detail.

Item internal consistency and item discriminant validity. Item internal consistency and item discriminant validity were tested by calculating the correlations of the items with their corresponding as well as with their non-corresponding dimensions. The corrected-correlations between the items and their corresponding dimensions were all >.65, which is beyond the acceptable level of .03 (see appendix II, table 4). Almost all of the items correlated higher with their corresponding dimension than with the non-corresponding dimensions, which supports item discriminant validity (see appendix II, table 4). Three items (item 4, 12 and 17) of three dimensions correlated equally high or slightly higher with a non-corresponding dimension. Two items (item 3 and 7) correlated the highest with their corresponding dimension, but also high with a non-corresponding dimension.

Distinctiveness and reliability of the dimensions. The distinctiveness of the dimensions was examined by analysing the correlations between the sumscores of the dimensions. A correlation of < .70 argues for a distinct construct and this was the case for the correlation between the sumscores of all dimensions, except that the correlations between the physical and living with dimension (r = .76) and living with and cognitive dimension (r = .77) were higher than the acceptable level of .70 (see table 4).

The reliability estimates of the dimensions of fatigue were high, namely physical fatigue (λ_2 = .83), living with fatigue (λ_2 = .92), cognitive fatigue (λ_2 = .90) and emotional fatigue (λ_2 = .84) (see table 4).

Table 4. Spearman Rho correlation between sumscores of the dimensions of fatigue of the BRAF-MDQ

Dimensions	Physical	Living with	Cognitive	Emotional
Physical		0.76	0.65	0.65
Living with			0.77	0.67
Cognitive				0.68
Emotional				
Reliability estimates	.83	.92	.90	.84

External construct validity. As expected, the correlations between the dimensions of fatigue and the variables age and disease duration were weak (< .30 and <-.30), thus the hypotheses of divergent validity were confirmed. All of the correlations between the variables of HRQoL and the dimension of fatigue were significant and at least moderate. As expected, the vitality scale of the SF-36 correlated strongly with the dimensions of fatigue. Thus the hypotheses of convergent validity were also confirmed (see table 5 for an overview of the correlations). The content of the relation between HRQoL and dimensions of fatigue is discussed in detail in the last paragraph of the method section.

Floor- and ceiling effects. The frequency of the scores on the dimensions showed that three dimensions were highly positively skewed, meaning there were relatively few high scores (see appendix II table 3). About one third of the patients scored the minimum score zero on the living with dimension, 45 % on cognitive dimension and 53 % on the emotional dimension. In other words, all dimensions, except for the physical dimension, showed floor-effects (see appendix II table 3).

To answer the second research question, the multidimensional structure of the BRAF-MDQ is broadly confirmed by the PCA. Overall, the values of item internal consistency and item discriminant validity support the dimensional structure. The dimensions seem to be reliable, but the distinctiveness of the living with fatigue dimension was less stable, due to crossloadings of some items with other dimensions. The relation with other variables was as expected, which supports construct validity. Major shortcomings are the floor effects of the living with, cognitive and emotional dimensions.

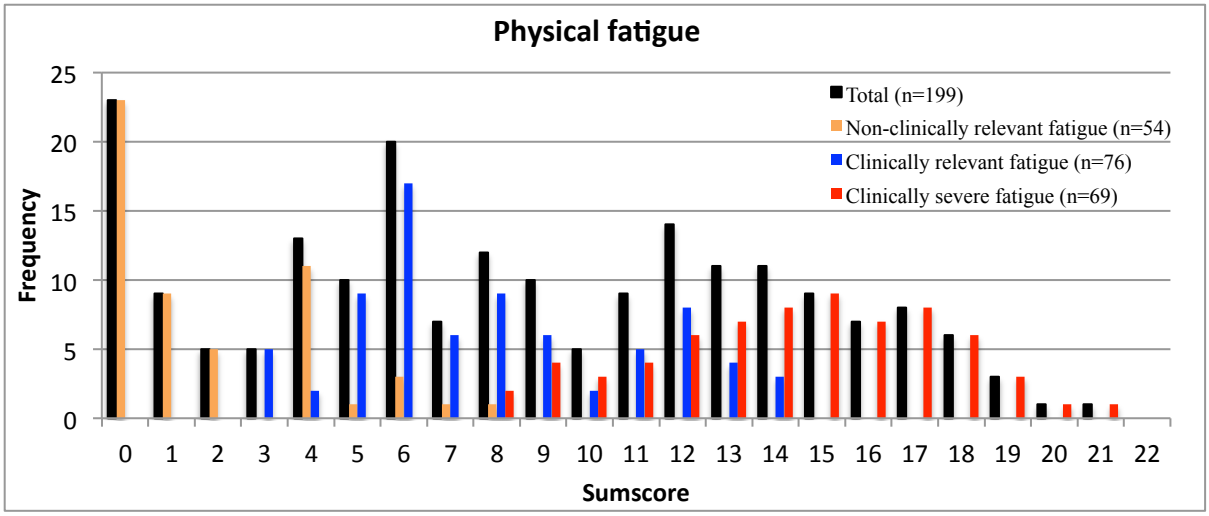
Exploration of possible (significant) differences in scores on the dimensions of fatigue between patients with different severities of fatigue.

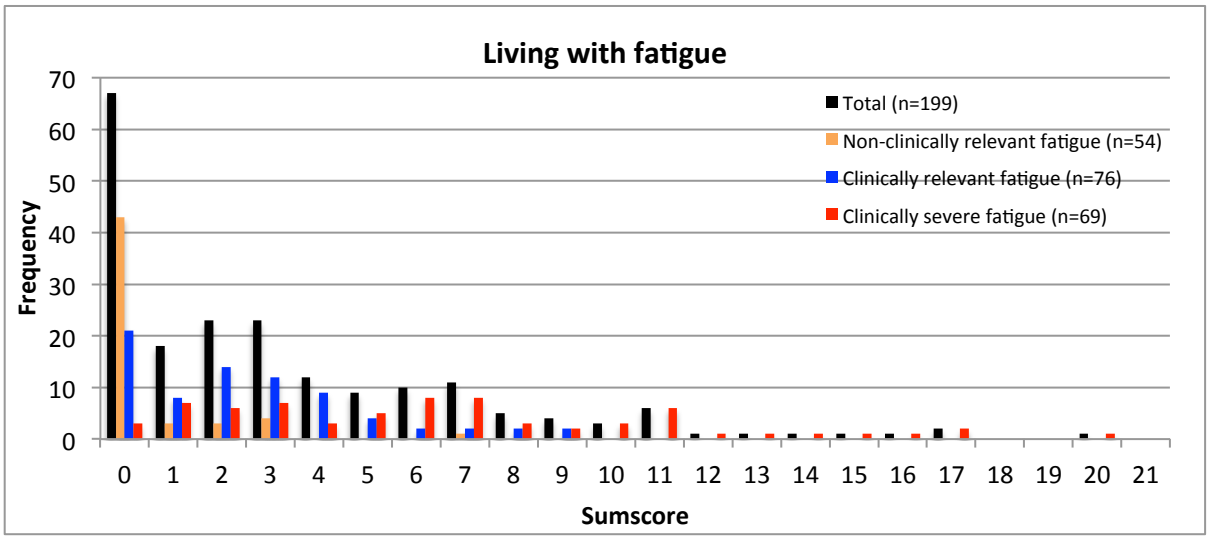
When the frequency and distribution of the scores on each fatigue dimension for the total sample were visually compared to the frequency and distribution of the scores for patients with different severities of fatigue, totally different distribution patterns are shown (see figure 2). Splitting up the results for patients with different severities of fatigue was based on the scores on the BRAF NRS severity of fatigue. This led to the following three groups: patients with non-clinically relevant fatigue (BRAF NRS score of < 2), clinically relevant fatigue (BRAF NRS score of ≥ 2 < 5) and clinically severe fatigue (BRAF NRS score of ≥ 5).

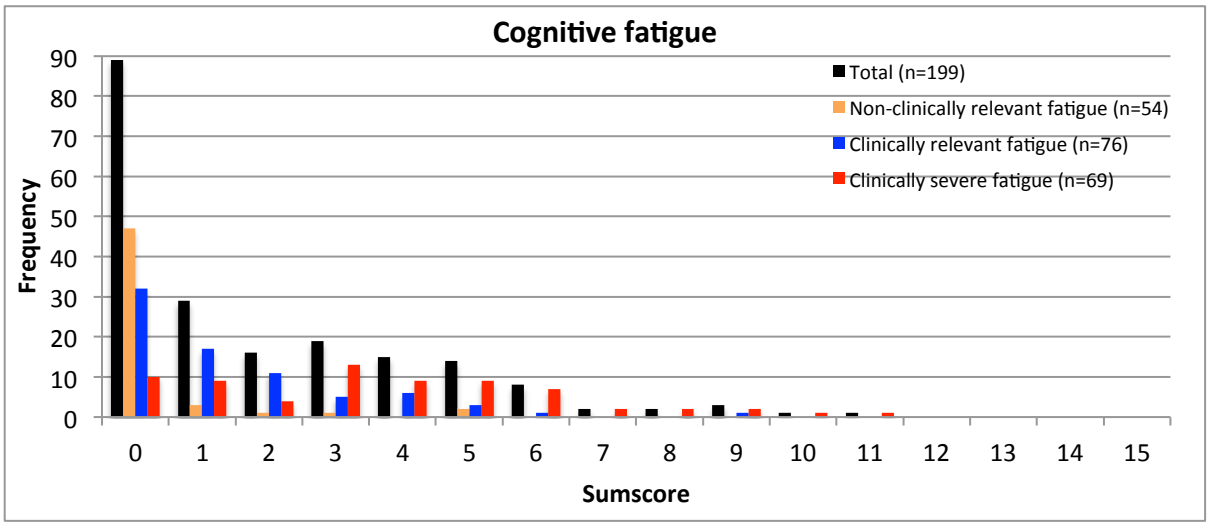
The Kruskal-Wallis test showed that the frequency of fatigue scores on the dimensions differed significantly between patients with non-clinically relevant, clinically relevant and clinically severe fatigue, with physical fatigue ($H(2) = 149.519$, $p < .001$), living with fatigue ($H(2) = 87.579$, $p < .001$), cognitive fatigue ($H(2) = 71.518$, $p < .001$) and emotional fatigue ($H(2) = 71.463$, $p < .001$).

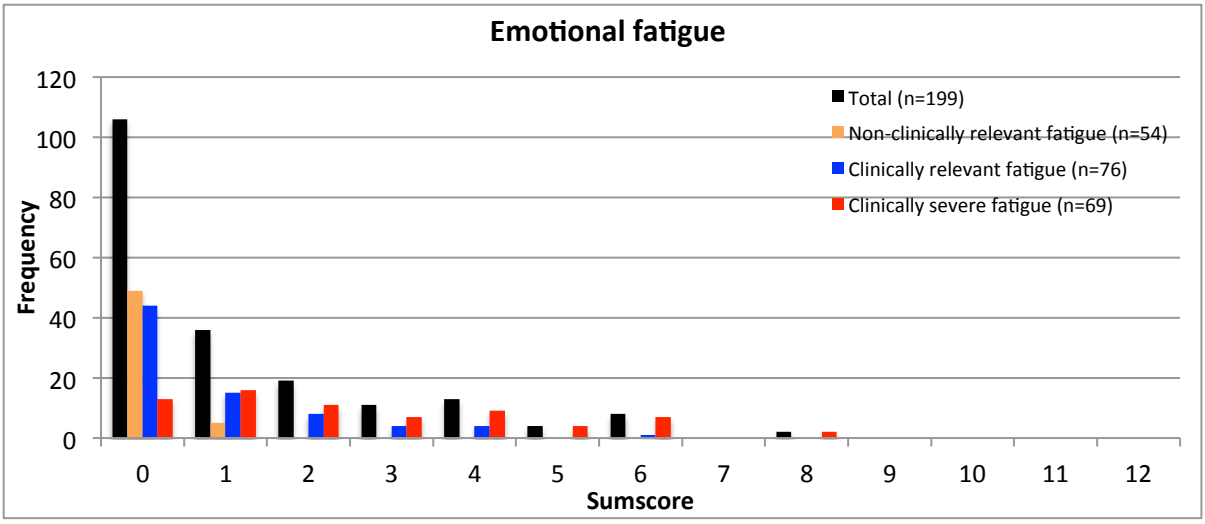
In order to answer the third research question, results of the Mann-Whitney tests with a Bonferonni correction of $p < .0167$ showed that patients with clinically severe fatigue scored significantly higher at each fatigue dimension than patients with clinically relevant fatigue. And patients with clinically relevant fatigue scored significantly higher at each fatigue dimension than patients with non-clinically relevant fatigue (see appendix II table 5).

Figure 2. Frequency and distribution of scores on the dimensions of fatigue









How dimensions of fatigue are related to disease activity and variables of HRQoL

The correlation coefficient between disease activity and dimensions of fatigue ranged from .05 to .09. Significant moderate to strong correlations were found between the dimensions of fatigue and variables of HRQoL (see table 5). The following features stood out when looking at the possible differences between the dimensions in strength of relation with the variables of HRQoL.

Firstly, the living with fatigue dimension correlated the strongest with physical functioning, role-physical functioning and social functioning compared to the other dimensions (see the bold displayed correlation coefficients in table 5). This is conforming the theoretical background, because this fatigue dimension represents the impact of fatigue on daily and social life.

Secondly, limitations in emotional role functioning and mental health were most strongly related to emotional fatigue, which is also understandable considering the theoretically conformity. However, the least strong, but still moderate relations were shown between all dimensions of fatigue and limitations in emotional role functioning and mental health (see the bold displayed correlation coefficients in table 5). This suggests that multidimensional fatigue is less associated with the extent of feeling down or anxious, in comparison to the way fatigue is associated with other variables of HRQoL. The cognitive dimension did not correlate the least strong with the variables of HRQoL, which is contradicting to our expectation.

To answer the final research question, the results showed that disease activity is not related to the dimensions of fatigue. Concerning the content of the relations between dimensions of

fatigue and variables of HRQoL, at least significant moderate relations were shown between all dimensions and variables of HRQoL. The living with and the emotional dimension correlated stronger than the other dimensions with those variables of HRQoL that had the strongest theoretically conformity.

Table 5. Correlates of the dimensions of fatigue

	Dimensions of fatigue			
	Physical	**Living with**	**Cognitive**	**Emotional**
Patient characteristics				
Age	-.14*	-.02	.05	-.11
Disease characteristics				
Disease activity	.09	.06	.06	.05
Disease duration	.00	.01	.02	-.03
Health related quality of life				
Physical functioning	-.55**	**-.64****	-.52**	-.41**
Role physical	-.56**	**-.64****	-.52**	-.47**
Bodily pain	-.63**	-.61**	-.50**	-.48**
General health	-.52**	-.49**	-.47**	-.54**
Social functioning	-.59**	**-.64****	-.63**	-.59**
Role emotional	-.34**	-.42**	-.37**	**-.44****
Mental health	-.36**	-.35**	-.43**	**-.50****
Vitality	-.74**	-.74**	-.66**	-.65**

Note. Higher scores on the dimensions of fatigue indicated more fatigue; Higher scores on the HRQoL variables indicated better HRQoL;** one-sided p-value ≤ 0.01; * one-sided p-value ≤ 0.05. Bold displayed correlation coefficients are described in the text in more detail.

Discussion

This is not only the first study that examined the relation between disease activity and multidimensional fatigue in RA patients with predominantly low disease activity, but it is also the first study that evaluated the psychometric properties of the Dutch translation of the BRAF-MDQ.

First, the prevalence of fatigue was examined, in order to examine to what extend clinically relevant levels of fatigue were present in RA patients with predominantly low disease activity. The scores on a BRAF NRS severity of fatigue indicated that 73 % of the patients experienced clinically relevant levels of fatigue even though 96 % of the patients had low disease activity. These results are consistent with previous prevalence rates of fatigue in RA, which ranged from 42 to 90 % depending on the chosen fatigue measures (Belza, et al., 1993; Kalyoncu, et al., 2009; Pollard, et al., 2006; Repping-Wuts, et al., 2008; Rupp, et al., 2004; Wolfe, et al., 1996; Yacoub Ibn, et al., 2012). What distinguishes our study from these previous studies is the preselected sample of RA patients with low disease activity, which means that inflammation is at a minimum level for these patients. Our findings indicate that even though inflammation is clinically under control, the majority of the patients still report clinically relevant fatigue.

Second, the BRAF-MDQ was used to assess the relation between disease activity and multiple dimensions fatigue. Since the Dutch translation of the BRAF-MDQ had not been validated yet, a psychometric evaluation was conducted first. The four-dimensional structure as postulated by the developers (Nicklin, et al., 2010a), was broadly confirmed. The distinctiveness of the living with fatigue dimension was less stable, due to cross-loading of some items on the physical and emotional dimension. This was also revealed in initial results of the multiple rounds of factor analysis, which reduced a draft 45-item into a final 20-item questionnaire, described in detail in the thesis of Nicklin (Nicklin, 2009). Other anomalies were found for one item of the cognitive dimension (Have you lacked mental energy because of fatigue?) and one item of the emotional dimension (Have you felt you have less control because of fatigue?). These items loaded higher on each other's dimensions than on their own dimension. This might be explained by the following, 'a lack of mental energy' and 'less control' could be interpreted in more than one way and are possibly not specific enough. This was also the comment of patients and professionals included in a Dutch Delphi study that evaluated the content validity of the BRAF-MDQ (Nikolaus, Bode, Taal, & van der Laar, 2012). A psychometric shortcoming of the BRAF-MDQ was the major floor effects that were found on the living with (34 % of the patients scored 0), cognitive (45 % of the patients

scored 0) and emotional dimension (53 % of the patients scored 0), which is psychometrically undesirable due to lack of distinctiveness. To conclude, the four-dimensional structure of the BRAF-MDQ was satisfactory, but the BRAF-MDQ is probably not the most appropriate fatigue measure for this specific RA sample, due to the major floor effects.

In contrast to the high scores on the BRAF NRS severity of fatigue, scores on the different fatigue dimensions (measured with the BRAF-MDQ) were relatively low. Nicklin et al. (2010a) also reported a non-normal distribution of the BRAF-MDQ, but their distribution was less skewed than the distribution in this study. The most obvious explanation is that Nicklin et al. (2010a) only included patients with clinically severe fatigue scores (VAS fatigue score of ≥ 5). This explanation was verified as the third aim of the study, by analysing the differences in frequency and distribution of the scores on the different dimensions of fatigue between patients with non-clinically relevant fatigue, clinically relevant fatigue and clinically severe fatigue.

The results showed that patients with clinically severe fatigue scored significantly higher at each fatigue dimension than patients with clinically relevant fatigue. And patients with clinically relevant fatigue scored significantly higher at each fatigue dimension than patients with non-clinically relevant fatigue. This means that although patients experience some degree of fatigue, it does not necessarily interfere with daily, social, emotional and cognitive life. It seems that RA patients in general are susceptible to experiencing fatigue, but as severity of fatigue increases, it becomes more complex and unfolds itself in different aspects of life. The aforementioned is the most striking result of this study and has not yet been demonstrated in previous studies.

The final aim of this study was to determine how the dimensions of fatigue are related to disease activity and variables of HRQoL. Due to conflicting results in previous research regarding the relation between fatigue and disease activity (Nikolaus, et al., 2013a), no expectations were formulated. In contrast to Hewlett et al. (2011a), they made a hypothetical model of the causal pathways of fatigue, whereby the group of disease-related factors of RA (including factors of disease activity) is one of the three overarching, interacting factors that may cause RA fatigue. As the developers of this model argued, the evidence on causality of RA fatigue is incomplete and this model should be used to formulate and test hypotheses.

This study showed that the correlation coefficients between disease activity and dimensions of fatigue ranged from .05 to .09, which indicated that disease activity is not related to the dimensions of fatigue in RA patients with predominantly low disease activity. In

other words, the hypothetical model of Hewlett et al. (2011a) might not be fully applicable for this specific RA sample.

Regarding the association between multidimensional fatigue and variables of HRQoL, our hypotheses about a moderate to strong relation between multidimensional fatigue and variables of HRQoL were confirmed. This study supports the notion that variables of HRQoL, including physical functioning and pain and psychosocial variables are related to fatigue, rather than disease activity. These findings were also reported in previous studies (Huyser, et al., 1998; Pollard, et al., 2006; van Hoogmoed, et al., 2010). The developers of the BRAF-MDQ argued for separate fatigue dimensions (Nicklin, et al., 2010a), thus we expected that the fatigue dimensions would relate differently to the variables of HRQoL. These differences were shown for two dimensions. First, the living with fatigue dimension was most strongly related to physical functioning, role-physical functioning and social functioning, which support the theoretical conformity of this dimension, because it is supposed to represent the impact of fatigue on daily and social life. Second, the emotional dimension correlated stronger than the other dimensions with emotional-role functioning and mental health, which is also conforming the theory, because the emotional dimension represents the way fatigue affects feelings.

Another striking feature was the least strong, but still moderate relation, between all fatigue dimensions and limitations in emotional role functioning and mental health. It suggested that fatigue is less associated with the extent of feeling down or anxious, in comparison to the way fatigue is associated with decrease in daily physical and social activities, increase in the extent of pain and decrease in vitality and general health. This is in contrast to some previous studies, which showed that depression and/or anxiety are the "best" predictors of, or most closely related to, severity of fatigue (Huyser, et al., 1998; Lisitsyna et al., 2013; Pollard, et al., 2006).

However, the differences between the dimensions were not as convincing as the differences that were found in the study of Nicklin et al. (2010a). They found, compared to our study, major differences between the dimensions in strength of correlations with daily functioning, pain, mood and anxiety. An explanation for this would be that the sumscores on the different dimensions were relatively low in our study. We sought for differences between dimensions, even though the majority of the patients did not experience fatigue at different dimensions.

This study has several implications. Due to the lack of cut-off criteria of the BRAF-MDQ, it was impossible to make judgements about the severity of fatigue. Therefore, cut-off scores of the BRAF NRS severity of fatigue were used to answer the first and third research question. These cut-off scores were not validated, but were derived from frequently used cut-off scores of the VAS fatigue (Nicklin, et al., 2010a; Pollard, et al., 2006). Although the BRAF NRS severity of fatigue and the VAS fatigue showed strong correlation in a previous study (r = .78), they are not interchangeable due to slightly higher mean scores of the BRAF NRS severity of fatigue (mean 6.8 and SD 1.8) compared to the mean scores of the VAS fatigue (mean 6.7 and SD 1.8) (Nicklin, et al., 2010a). Therefore, the use of these criteria was not fully justified, however the use of the BRAF NRS severity of fatigue is preferable to the use of the VAS fatigue due to lack of standardization of the wording of the VAS fatigue.

The results of our study, then, indicated that disease activity did not play a role in the large and complex network of multiple interacting factors that could cause fatigue in this particular sample of RA patients. Nevertheless, this statement about the influence of disease activity on fatigue needs to be made with some precaution, considering the cross-sectional design of this study and due to the preselected sample with predominantly low disease activity. On the one hand this sample might lead to deceptive results about the relation between disease activity and multidimensional fatigue, but on the other hand fatigue is highly prevalent in this sample, which indicates that fatigue is indeed more than an inflammation-related symptom.

The major floor effects of the living with, emotional and cognitive fatigue dimensions and the limited variance in the multidimensional fatigue scores made the data less suitable for studying the relation with other variables. Considering that this is the first study that psychometrically evaluated the Dutch translation of the BRAF-MDQ and the first study that analysed the content of these relations in this specific RA sample, it is a first step that invites others to proceed.

The strengths of this study are the use of a multidimensional fatigue measure is assessing the relation with disease activity and variables of HRQoL. We also were the first that studied the relation between disease activity and multidimensional fatigue in RA patient with low disease activity and this is the first psychometrically evaluation of the Dutch translation of the BRAF-MDQ. Moreover did we show new insights into the origin of multidimensional fatigue.

To sum up, the findings indicate that even though disease activity is clinically under control, the majority of the patients still reported clinically relevant levels of fatigue. The four-dimensional structure of the BRAF-MDQ is broadly confirmed, but the BRAF-MDQ is probably not the most appropriate measure for this specific RA sample, due to the major floor effects. Significant differences were found on the scores at the dimensions between patients with different severities of fatigue that indicated that the likelihood of experiencing multidimensional fatigue increases as severity of fatigue increases. Not disease activity, but variables of HRQoL were significantly related to multidimensional fatigue.

The first recommendation for future research would be that fatigue must be addressed more frequently in daily practice and research. Even though the interest in RA fatigue has increased over the last decade, fatigue is still not a core outcome measure in RA studies, it is not a criterion for remission and patients feel they get insufficient support from their health care professional and therefore have to manage it alone, often unsuccessfully (Felson, et al., 2011; Hewlett, et al., 2005; Repping-Wuts, et al., 2009). The prevalence rates of this study, once again, showed that fatigue is a major issue for RA patients even when disease activity is low, thus it should be, like many other researchers suggest, included as core outcome measure in all clinical trials (Felson, et al., 2011; Hewlett, et al., 2011b; Kirwan & Hewlett, 2007; Wells, 2009).

Until today, evidence about the possible causes and consequences of RA fatigue is incomplete and inconsistent. It is most likely that fatigue is caused by multiple, circular and interacting factors that vary between and within individuals (Nikolaus, et al., 2013a). This not only means that multiple factors could predict fatigue, but that they could also be predicted by fatigue (Hewlett et al., 2011a; Nikolaus, et al., 2013a). Longitudinal studies that consist of representative samples, use a validated multidimensional fatigue measure and apply multivariate analysis would be the most optimal way to study these causal pathways of multidimensional fatigue (Nikolaus, et al., 2013a).

Subsequently, the nature of multidimensional fatigue should be analysed in more detail. Our finding about the plausible transformation from general, unspecified fatigue into multidimensional fatigue should also be further explored in future research, for example by qualitative methods such as focus groups or in-depth interviews, or by quantitative methods like studying the progress of fatigue over time in combinations with its correlates such as feelings of depression, sleep disturbance, pain and HRQoL (Franklin & Harrell, 2013;

Lisitsyna, et al., 2013; Pollard, et al., 2006; Thyberg, et al., 2009; van Hoogmoed, et al., 2010).

Nowadays, if fatigue is already included as outcome measure, it is most often studied with a single-item fatigue measure (Hewlett, et al., 2011b). This measure is suitable for a quick screening of the severity of fatigue, but does not give insights in all aspects and the impact of fatigue (Hewlett, et al., 2011b). Patients describe fatigue as different from normal tiredness and some report, for example, that it is impossible to think clearly, to work or to participate in social activities due to fatigue (Hewlett, et al., 2005; Repping-Wuts, et al., 2008). A VAS fatigue score of '7' could therefore mean a variety of things. A psychometrically sound multidimensional fatigue measure takes all facets of fatigue into account and is therefore preferable to a one-dimensional measure. It is therefore necessary to further validate and improve the psychometric properties of the BRAF-MDQ, especially defining cut-off criteria. When these cut-off criteria are specified, this instrument could be used for several interesting objectives in daily practice as well as in research. In daily practice the BRAF-MDQ can be used to get more insight into the specifics of fatigue for a particular patient, which can be useful in choosing an appropriate intervention. In research further exploration of the aetiology of fatigue, effectiveness of interventions and progress of fatigue could also be measured by using the BRAF-MDQ.

An alternative to the current way of measurement is the more advanced and more precise way of measurement called computer-adaptive testing (CAT). CAT is a relatively new way of measurement in which each question is selected from a large item bank, based on the respondent's responses to previous questions. CAT makes use of models of item-response theory (IRT) which lead to an unique tailored testing experience for the respondent (Kantrowitz, Dawson, & Fetzer, 2011). A major advantage of CAT is the possibility of developing a large item bank, which covers all facets of fatigue. Due to this more precise way of measurement the chance of detecting floor- or ceiling effects is almost ruled out. Due to the tailored way of delivery, the respondent does not have to answer a fixed number of questions, it is therefore most likely less time-consuming compared to the pencil and paper questionnaires. To date, there is no computer-adaptive test available for fatigue in RA, but soon there will be. Nikolaus et al. (2013b) made the first move by constructing an item bank of multidimensional fatigue in RA. Their initial analysis led to an item bank that consists of 196 items, including 18 items of the BRAF-MDQ (Nikolaus et al., 2013b). We are looking forward to the progress of this new way of fatigue measurement in RA.

The discussion section in a nutshell: The findings indicate that even though RA inflammation is clinically under control, the majority of the patients still reported clinically relevant fatigue Longitudinal studies are needed to further our understanding of the causal pathways of RA fatigue. Based on our findings, we suggest that fatigue does not necessarily interfere with patients' daily, social, emotional and cognitive life. But as severity of fatigue increases, it becomes more complex and unfolds itself in different aspects of life. Although the four-dimensional structure of the BRAF-MDQ is broadly confirmed, the major floor effects point to possibilities for improvement of fatigue measurement by, for example, computer adaptive testing.

References

Arnett, F. C., Edworthy, S. M., Bloch, D. A., McShane, D. J., Fries, J. F., Cooper, N. S., et al. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism, 31*(3), 315-324.

Belza, B. L., Henke, C. J., Yelin, E. H., Epstein, W. V., & Gilliss, C. L. (1993). Correlates of fatigue in older adults with rheumatoid arthritis. *Nursing Research, 42*(2), 93-99.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (Second edition ed.). New York: Lawrence Erlbaum Associates.

Contreras-Yanez, I., Cabiedes, J., Villa, A. R., Rull-Gabayet, M., & Pascual-Ramos, V. (2010). Persistence on therapy is a major determinant of patient-, physician- and laboratory-reported outcomes in recent-onset rheumatoid arthritis patients. *Clinical and Experimental Rheumatology, 28*(5), 748-751.

Dhir, V., Lawrence, A., Aggarwal, A., & Misra, R. (2009). Fibromyalgia is common and adversely affects pain and fatigue perception in North Indian patients with rheumatoid arthritis. *Rheumatology, 36*, 2443-2448.

Dupond, J. L. (2011). Fatigue in patients with rheumatic diseases. *Joint Bone Spine, 78*(2), 156-160.

Dures, E. K., Hewlett, S. E., Cramp, F. A., Greenwood, R., Nicklin, J. K., Urban, M., et al. (2013). Reliability and sensitivity to change of the Bristol Rheumatoid Arthritis Fatigue Scales. *Rheumatology*.

Feldthusen, C., Björk, M., Forsblad-d'Elia, H., & Mannerkorpi, K. (2012). Perception, consequences, communication, and strategies for handling fatigue in persons with rheumatoid arthritis of working age-a focus group study. *Clinical Rheumatology*, 1-10.

Felson, D. T., Smolen, J. S., Wells, G., Zhang, B., van Tuyl, L. H. D., Funovits, J., et al. (2011). American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials. [Article]. *Annals of the Rheumatic Diseases, 70*(3), 404-413.

Field, A. (2009). *Discovering statistics using SPSS* (Third edition ed.). London: SAGE Publications Ltd.

Franklin, A. L., & Harrell, T. H. (2013). Impact of fatigue on psychological outcomes in adults living with rheumatoid arthritis. *Nursing Research, 62*(3), 203-209.

Fuchs, H. A. (1993). The use of the disease activity score in the analysis of clinical trials in rheumatoid arthritis. *Journal of Rheumatology, 20*(11), 1863-1866.

Gestel v. AM, H. C., Riel v. PL. (1998). Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum, 41*(10), 1845-1850.

Hewlett, S., Cockshott, Z., Byron, M., Kitchen, K., Tipler, S., Pope, D., et al. (2005). Patients' perceptions of fatigue in rheumatoid arthritis: Overwhelming, uncontrollable, ignored. *Arthritis & Rheumatism-Arthritis Care & Research, 53*(5), 697-702.

Hewlett, S., Hehir, M., & Kirwan, J. R. (2007). Measuring fatigue in rheumatoid arthritis: A systematic review of scales in use. *Arthritis & Rheumatism-Arthritis Care & Research, 57*(3), 429-439.

Hewlett, S., Chalder, T., Choy, E., Cramp, F., Davis, B., Dures, E., et al. (2011a). Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology, 50*(6), 1004-1006.

Hewlett, S., Dures, E., & Almeida, C. (2011b). Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for Severity, Effect, and Coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi. *Arthritis Care and Research, 63*(SUPPL. 11), S263-S286.

Huyser, B. A., Parker, J. C., Thoreson, R., Smarr, K. L., Johnson, J. C., & Hoffman, R. (1998). Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis and Rheumatism, 41*(12), 2230-2237.

IBM. (2011). SPSS statistics for macintosh (Version Version 20.0). Armonk: NY: IBM Corp.

Kalyoncu, U., Dougados, M., Daurès, J. P., & Gossec, L. (2009). Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: A systematic literature review. *Annals of the Rheumatic Diseases, 68*(2), 183-190.

Kantrowitz, T., Dawson, C., & Fetzer, M. (2011). Computer Adaptive Testing (CAT): A Faster, Smarter, and More Secure Approach to Pre-Employment Testing. *Journal of Business and Psychology, 26*(2), 227-232.

Kirwan, J. R., & Hewlett, S. (2007). Patient perspective: Reasons and methods for measuring fatigue in rheumatoid arthritis. *Journal of Rheumatology, 34*(5), 1171-1173.

Lisitsyna, T. A., Veltishchev, D. Y., Gerasimov, A. N., Seravina, O. F., Kovalevskaya, O. B., Zeltyn, A. E., et al. (2013). The magnitude of fatigue and its association with depression, pain, and inflammatory activity in rheumatoid arthritis. *Terapevticheski«ê arkhiv, 85*(5), 8-15.

Nicklin, J. (2009). *The development of scales to measure fatigue in RA*. Universitiy of the West of England, Bristol, UK.

Nicklin, J., Cramp, F., Kirwan, J., Greenwood, R., Urban, M., & Hewlett, S. (2010a). Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. *Arthritis care & research, 62*(11), 1559-1568.

Nicklin, J., Cramp, F., Kirwan, J., Urban, M., & Hewlett, S. (2010b). Collaboration with patients in the design of patient-reported outcome measures: capturing the experience of fatigue in rheumatoid arthritis. *Arthritis care & research, 62*(11), 1552-1558.

Nikolaus, S., Bode, C., Taal, E., & van der Laar, M. (2012). Expert evaluations of fatigue questionnaires used in rheumatoid arthritis: a Delphi study among patients, nurses and rheumatologists in the Netherlands. *Clinical and Experimental Rheumatology, 30*(1), 79-84.

Nikolaus, S., Bode, C., Taal, E., & van de Laar, M. A. F. J. (2013a). Fatigue and factors related to fatigue in rheumatoid arthritis: A systematic review. *Arthritis care & research, 65*(7), 1128-1146.

Nikolaus, S., Bode, C., Taal, E., Oostveen, J. C. M., Glas, C. A. W., & van de Laar, M. A. F. J. (2013b). Items and dimensions for the construction of a multidimensional computerized adaptive test to measure fatigue in patients with rheumatoid arthritis. *Journal of Clinical Epidemiology, 66*(10), 1175-1183.

Oncu, J., Basoglu, F., & Kuran, B. (2013). A comparison of impact of fatigue on cognitive, physical, and psychosocial status in patients with fibromyalgia and rheumatoid arthritis. *Rheumatology International*, 1-7.

Pollard, L. C., Choy, E. H., Gonzalez, J., Khoshaba, B., & Scott, D. L. (2006). Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology, 45*(7), 885-889.

Prevoo, M. L. L., Van 'T Hof, M. A., Kuper, H. H., Van Leeuwen, M. A., Van De Putte, L. B. A., & Van Riel, P. L. C. M. (1995). Modified disease activity scores that include twenty-eight-joint counts: Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis and Rheumatism, 38*(1), 44-48.

Repping-Wuts, H., Fransen, J., Van Achterberg, T., Bleijenberg, G., & Van Riel, P. (2007). Persistent severe fatigue in patients with rheumatoid arthritis. *Journal of Clinical Nursing, 16*(11C), 377-383.

Repping-Wuts, H., Uitterhoeve, R., van Riel, P., & van Achterberg, T. (2008). Fatigue as experienced by patients with rheumatoid arthritis (RA): A qualitative study. *International Journal of Nursing Studies, 45*(7), 995-1002.

Repping-Wuts, H., Van Riel, P., & Van Achterberg, T. (2009). Fatigue in patients with rheumatoid arthritis: What is known and what is needed. *Rheumatology, 48*(3), 207-209.

Rupp, I., Boshuizen, H. C., Jacobi, C. E., Dinant, H. J., & Van Den Bos, G. A. M. (2004). Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis Care and Research, 51*(4), 578-585.

Sijtsma, K. (2009). On the use, the misuse, and the very limited usefulness of Cronbach's alpha. *Psychometrika, 74*(1), 107-120.

Singh, J. A., Christensen, R., Wells, G. A., Suarez-Almazor, M. E., Buchbinder, R., Lopez-Olivo, M. A., et al. (2009). Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*(4).

Staud, R. (2012). Peripheral and central mechanisms of fatigue in inflammatory and noninflammatory rheumatic diseases. *Current Rheumatology Reports, 14*(6), 539-548.

Stebbings, S., Herbison, P., Doyle, T. C. H., Treharne, G. J., & Highton, J. (2010). A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: disparity in associations with disability, anxiety and sleep disturbance. *Rheumatology, 49*(2), 361-367.

Tack, B. B. (1990). Fatigue in rheumatoid arthritis: Conditions, strategies, and consequences. *Arthritis Care and Research, 3*(2), 65-70.

ten Klooster, P. M., Vonkeman, H. E., Taal, E., Siemons, L., Hendriks, L., de Jong, A. J. L., et al. (2013). Performance of the Dutch SF-36 version 2 as a measure of health-related quality of life in patients with rheumatoid arthritis. *Health and Quality of Life Outcomes, 11*(1).

Terwee, C. B., Bot, S. D. M., de Boer, M. R., van der Windt, D. l. A. W. M., Knol, D. L., Dekker, J., et al. (2007). Quality criteria were proposed for measurement properties of health status questionnaires. *Journal of Clinical Epidemiology, 60*(1), 34-42.

Thyberg, I., Dahlström, O., & Thyberg, M. (2009). Factors related to fatigue in women and men with early rheumatoid arthritis: The swedish tira study. *Journal of Rehabilitation Medicine, 41*(11), 904-912.

Van Dartel, S. A. A., Repping-Wuts, J. W. J., Van Hoogmoed, D., Bleijenberg, G., Van Riel, P. L. C. M., & Fransen, J. (2013). Association between fatigue and pain in rheumatoid

arthritis: Does pain precede fatigue or does fatigue precede pain? *Arthritis Care and Research, 65*(6), 862-869.

van Hoogmoed, D., Fransen, J., Bleijenberg, G., & van Riel, P. (2010). Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology, 49*(7), 1294-1302.

Wells, G. A. (2009). Patient-Driven Outcomes in Rheumatoid Arthritis. *Journal of Rheumatology, 36*, 33-38.

Wolfe, F., Hawley, D. J., & Wilson, K. (1996). The prevalence and meaning of fatigue in rheumatic disease. *Journal of Rheumatology, 23*(8), 1407-1417.

Yacoub Ibn, Y., Amine, B., AssiaLaatiris, B., Wafki, F., Znat, F., & Hajjaj-Hassouni, N. (2012). Fatigue and severity of rheumatoid arthritis in moroccan patients. *Rheumatology International, 32*(7), 1901-1907.

Appendix I

Multidimensionale Bristol-vragenlijst over vermoeidheid bij reumatoïde artritis (BRAF-MDQ)

Wij willen graag weten welke invloed vermoeidheid op u heeft gehad in de afgelopen 7 dagen. Wilt u alstublieft alle vragen beantwoorden? Denk er niet te lang en te diep over na, maar geef uw eerste reactie – er zijn geen goede of foute antwoorden!

1. Omcirkel het cijfer dat uw gemiddelde vermoeidheidsniveau weergeeft in de afgelopen 7 dagen.

Geen vermoeidheid 0 1 2 3 4 5 6 7 8 9 10 Volledig uitgeput

Vink voor elk van de volgende vragen één antwoord aan dat het best op u van toepassing is.

2. Hoeveel dagen hebt u vermoeidheid ervaren in de afgelopen week (7 dagen)?

0	☐	4	☐
1	☐	5	☐
2	☐	6	☐
3	☐	Elke dag	☐

3. Hoe lang duurde elke periode van vermoeidheid gemiddeld de afgelopen 7 dagen?

Minder dan een uur	☐
Meer dan een uur, maar niet de hele dag	☐
De hele dag	☐

De afgelopen 7 dagen.....	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
4. Had u te weinig *lichamelijke* energie vanwege vermoeidheid?	☐	☐	☐	☐

	De afgelopen 7 dagen.....	Helemaal niet	Een beetje	Nogal	Heel erg
5.	Had u moeite met in bad gaan of douchen vanwege vermoeidheid?	☐	☐	☐	☐
6.	Had u moeite met het aankleden vanwege vermoeidheid?	☐	☐	☐	☐
7.	Had u moeite met het uitoefenen van uw werkzaamheden of andere dagelijkse activiteiten vanwege vermoeidheid?	☐	☐	☐	☐
8.	Hebt u het maken van plannen vermeden vanwege vermoeidheid? Bijvoorbeeld: plannen om uit te gaan, of klusjes in huis of tuin te doen.	☐	☐	☐	☐
9.	Heeft vermoeidheid uw sociale leven beïnvloed?	☐	☐	☐	☐
10.	Hebt u plannen geannuleerd vanwege vermoeidheid? Bijvoorbeeld: plannen om uit te gaan, of klusjes in huis of tuin te doen.	☐	☐	☐	☐
11.	Hebt u uitnodigingen afgeslagen vanwege vermoeidheid? Bijvoorbeeld: afspreken met een vriend(in).	☐	☐	☐	☐
12.	Had u te weinig *geestelijke* energie vanwege vermoeidheid?	☐	☐	☐	☐
13.	Bent u dingen vergeten vanwege vermoeidheid?	☐	☐	☐	☐
14.	Kon u moeilijk helder denken vanwege vermoeidheid?	☐	☐	☐	☐
15.	Kon u zich moeilijk concentreren vanwege vermoeidheid?	☐	☐	☐	☐
16.	Hebt u vergissingen gemaakt vanwege vermoeidheid?	☐	☐	☐	☐
17.	Hebt u het gevoel gehad dat u minder controle had over bepaalde zaken in uw leven vanwege vermoeidheid?	☐	☐	☐	☐
18.	Voelde u zich in verlegenheid gebracht als gevolg van vermoeidheid?	☐	☐	☐	☐

19. Bent u van streek geweest als gevolg van vermoeidheid? ☐ ☐ ☐ ☐

20. Hebt u zich somber of depressief gevoeld vanwege vermoeidheid? ☐ ☐ ☐ ☐

Appendix II

Table 1. Hypotheses about strength of relations between dimensions of fatigue and patient and disease characteristics and HRQoL

	Dimensions of fatigue			
	Physical	**Living with**	**Cognitive**	**Emotional**
Patient characteristics				
Age	< -.30 < .30	< -.30 < .30	< -.30 < .30	< -.30 < .30
Disease characteristics				
Disease duration	< -.30 < .30	< -.30 < .30	< -.30 < .30	< -.30 < .30
Health-related quality of life				
Physical functioning	≥ -.30	**≥ -.30**	≥ -.30	≥ -.30
Role physical	≥ -.30	**≥ -.30**	≥ -.30	≥ -.30
Bodily pain	≥ -.30	≥ -.30	≥ -.30	≥ -.30
General health	≥ -.30	≥ -.30	≥ -.30	≥ -.30
Social functioning	≥ -.30	**≥ -.30**	≥ -.30	≥ -.30
Role emotional	≥ -.30	≥ -.30	≥ -.30	**≥ -.30**
Mental health	≥ -.30	≥ -.30	≥ -.30	**≥ -.30**
Vitality	≥ -.50	≥ -.50	≥ -.50	≥ -.50

Note. Higher fatigue scores indicated more fatigue and higher HRQoL scores indicated better HRQoL. Bold displayed correlations are described in the text in more detail.

Table 2. Distribution of responses for each item (n = 199)

		Response options												
Dimensions	Item	0	1	2	3	4	5	6	7	8	9	10	Mean	SD
Physical fatigue	1	24	30	30	30	16	19	18	22	8	2	0	3.43	2.47
	2	37	19	34	27	19	9	3	51	-	-	-	3.34	2.58
	3	72	110	18	-	-	-	-	-	-	-	-	0.73	0.62
	4	53	97	43	6	-	-	-	-	-	-	-	1.01	0.77
Living with fatigue	5	154	34	9	2	-	-	-	-	-	-	-	0.29	0.60
	6	164	26	8	1	-	-	-	-	-	-	-	0.23	0.54
	7	84	83	30	2	-	-	-	-	-	-	-	0.75	0.74
	8	89	75	31	4	-	-	-	-	-	-	-	0.75	0.79
	9	130	46	20	3	-	-	-	-	-	-	-	0.48	0.74
	10	124	55	15	5	-	-	-	-	-	-	-	0.50	0.75
	11	150	37	10	2	-	-	-	-	-	-	-	0.32	0.62
Cognitive fatigue	12	120	61	16	2	-	-	-	-	-	-	-	0.50	0.69
	13	149	43	6	1	-	-	-	-	-	-	-	0.29	0.55
	14	130	60	9	0	-	-	-	-	-	-	-	0.39	0.58
	15	114	73	12	0	-	-	-	-	-	-	-	0.50	0.61
	16	158	40	1	0	-	-	-	-	-	-	-	0.21	0.42
Emotional fatigue	17	137	52	9	1	-	-	-	-	-	-	-	0.37	0.60
	18	153	38	8	0	-	-	-	-	-	-	-	0.27	0.53
	19	156	38	5	0	-	-	-	-	-	-	-	0.24	0.48
	20	140	50	9	0	-	-	-	-	-	-	-	0.34	0.56

Note. Higher scores indicated more fatigue

Table 3. Distribution of the sumscores of the BRAF-MDQ fatigue dimensions (n=199)

	Mean (SD)	% minimum score	Skewness (SE)	Kurtosis (SE)
Physical	8.51 (5.67)	12	0.10 (0.17)	-1.07 (0.34)
Living with	3.31 (3.95)	34	1.59 (0.17)	2.62 (0.34)
Cognitive	1.88 (2.39)	45	1.37 (0.17)	1.48 (0.34)
Emotional	1.22 (1.80)	53	1.65 (0.17)	2.13 (0.34)

Note. SD is standard deviation; SE is standard error.

Table 4. Item internal consistency and item discriminant validity (n = 199)

		Dimensions of fatigue			
Fatigue dimension	Item	Physical	Living with	Cognitive	Emotional
Physical	1	0.78	0.69	0.64	0.63
	2	0.75	0.67	0.57	0.55
	3	0.65	0.62	0.43	0.48
	4	0.72	0.72	0.60	0.60
Living with	5	0.52	0.71	0.52	0.44
	6	0.44	0.69	0.49	0.36
	7	0.75	0.76	0.70	0.62
	8	0.59	0.75	0.67	0.57
	9	0.61	0.81	0.66	0.60
	10	0.54	0.80	0.54	0.52
	11	0.46	0.77	0.58	0.56
Cognitive	12	0.55	0.66	0.66	0.58
	13	0.44	0.49	0.73	0.56
	14	0.52	0.65	0.84	0.62
	15	0.59	0.68	0.83	0.61
	16	0.45	0.45	0.65	0.48
Emotional	17	0.57	0.61	0.70	0.66
	18	0.46	0.55	0.57	0.66
	19	0.43	0.47	0.44	0.71
	20	0.45	0.45	0.47	0.70

Note. *Underlined correlations are corrected for overlap (correlation with the sum of the other items in the same scale).

Table 5. Differences in frequency between patients with non-clinically relevant fatigue (n=54), clinically relevant fatigue (n=76) and clinically severe fatigue (n=69), results of the Mann-Whitney U test.

	Mean rank	Median (P25-P75)	*p*-value
Physical fatigue			
Non-clinically vs. clinically	31.77 vs. 89.47	1.0 (0.0-4.0) vs. 7.0 (6.0-11.0)	< .01
Non-clinically vs. severe	27.57 vs. 88.99	1.0 (0.0-4.0) vs. 15.0 (12.0-17.0)	< .01
Clinically vs. severe	43.91 vs. 105.04	7.0 (6.0-11.0) vs. 15.0 (12.0-17.0)	< .01
Living with fatigue			
Non-clinically vs. clinically	44.19 vs. 80.64	0.0 (0.0-0.0) vs. 2.0 (0.0-4.0)	< .01
Non-clinically vs. severe	32.02 vs. 85.46	0.0 (0.0-0.0) vs. 6.0 (3.0 – 9.5)	< .01
Clinically vs. severe	54.14 vs. 93.77	2.0 (0.0-4.0) vs. 6.0 (3.0 – 9.5)	< .01
Cognitive fatigue			
Non-clinically vs. clinically	48.53 vs. 77.56	0.0 (0.0-0.0) vs. 1.0 (0.0-2.0)	< .01
Non-clinically vs. severe	35.43 vs. 82.80	0.0 (0.0-0.0) vs. 3.0 (1.0-5.0)	< .01
Clinically vs. severe	55.61 vs. 92.16	1.0 (0.0-2.0) vs. 3.0 (1.0-5.0)	< .01
Emotional fatigue			
Non-clinically vs. clinically	52.23 vs. 74.93	0.0 (0.0-0.0) vs. 0.0 (0.0-1.0)	< .01
Non-clinically vs. severe	35.34 vs. 82.86	0.0 (0.0-0.0) vs. 2.0 (1.0-4.0)	< .01
Clinically vs. severe	55.88 vs. 91.86	0.0 (0.0-1.0) vs. 2.0 (1.0-4.0)	< .01

Note. Non-clinically are patients with NRS severity of fatigue score of < 2; clinically are patients with NRS severity of fatigue score of ≥ 2 < 5; severe are patients with NRS severity of fatigue score of ≥ 5; P25 is 25th percentile; P75 is 75th percentile