# A multidimensional 'path analysis' model of factors explaining fatigue in rheumatoid arthritis

S.A.A. Rongen-van Dartel[1], H. Repping-Wuts[1], R. Donders[2], D. van Hoogmoed[1], H. Knoop[3], G. Bleijenberg[3], P.L.C.M. van Riel[4], J. Fransen[1]

*[1]Department of Rheumatology, Radboud University Medical Center, Nijmegen; [2]Department for Health Evidence, Radboud University Medical Center, Nijmegen; [3]Nijmegen Expert Centre for Chronic Fatigue, Radboud University Medical Center, Nijmegen; [4]Scientific Institute for Quality of Healthcare, Radboud University Medical Center, Nijmegen, The Netherlands.*

## Abstract

### Objective

*Fatigue is one of the most commonly reported symptoms in rheumatoid arthritis (RA). Many factors may play a causal role on fatigue in RA patients, but their contribution and interplay is barely understood. The objective was to develop a multidimensional model of factors that explain fatigue severity in RA.*

### Methods

*A cross-sectional study (n=228) of consecutive patients with RA was performed. Fatigue, disease characteristics and psychosocial and behavioural outcomes were collected. Baseline differences between non severely fatigued patients (CIS-fatigue <35) and severely fatigued patients (CIS-fatigue ≥35) were tested. Structural equation modeling was used to test a hypothesised model for fatigue.*

### Results

*The final model includes pain, physical functioning, mood, sense of control, sleep quality and fatigue, with good fit (CFI=0.976) explaining 74% of the variance in RA fatigue. Accordingly, poor sleep quality ($\beta$=0.42, p<0.001) and less physical functioning ($\beta$=0.65, p<0.001) are directly related to a higher level of fatigue. Less sense of control is related to more mood disturbance ($\beta$=0.64, p<0.001), more pain ($\beta$=0.389, p<0.001) and less physical functioning ($\beta$=-0.24, p<0.001). More mood disturbance is related to poor sleep quality ($\beta$=0.78, p<0.001) and higher pain level is related to less physical functioning ($\beta$=0.75, p<0.001).*

### Conclusion

*RA fatigue is directly influenced by poor sleep quality and physical functioning, and indirectly by sense of control, mood and pain. Treatment of these factors by psychological interventions and physical exercise could help to improve fatigue in patients with RA.*

**Key words**

fatigue, multidimensional model, treatment, rheumatoid arthritis.

*Sanne A.A. Rongen-van Dartel, PhD*
*Han Repping-Wuts, PhD*
*Rogier Donders, PhD*
*Dewy van Hoogmoed, MSc*
*Hans Knoop, MD, PhD*
*Gijs Bleijenberg, MD, PhD*
*Piet L.C.M. van Riel, MD, PhD*
*Jaap Fransen, PhD*

*Please address correspondence to:*
*Sanne A.A. Rongen-van Dartel,*
*Department of Rheumatology (470)*
*Radboud University Medical Center*
*P.O. Box 9101,*
*6500 HB Nijmegen, The Netherlands.*
*E-mail:*
*sanne.rongen-vandartel@radboudumc.nl*

*Received on March 12, 2015; accepted in revised form on July 27, 2015.*



*Funding: funding was provided by the Dutch Rheumatoid Arthritis Foundation.*

*Competing interests: none declared.*

## Introduction

Fatigue is a frequently reported symptom in rheumatoid arthritis (RA) (1) but its causes and their interplay are barely understood (2). Severe fatigue may occur in up to 40% of RA patients, even in patients with low and moderate levels of disease activity, who are reasonably well-treated regarding their RA (3). Currently, it is not clear which interventions are effective to treat RA fatigue. There is some evidence that psychological interventions as well as exercise may reduce fatigue in RA (4-6). Knowing which factors are associated with fatigue may guide choosing effective treatment options (2).

Inflammation, anaemia and depressive disorder have long be held responsible for fatigue in RA. However, the prevalence of anaemia and depression cannot explain the prevalence of severe fatigue in RA (7, 8). Although a positive association between disease activity and fatigue has been found (9-11), it appears that pain rather than inflammation is related to RA fatigue (1, 11-13). Consequently, the relation between inflammation and fatigue appears to be mediated through pain. Several cross-sectional studies showed that psychosocial factors, pain and limitations in daily functioning, rather than inflammation, are related to fatigue severity in RA (1, 9-12, 14-18). It has been shown that self reported depressive symptoms are associated with RA fatigue (11, 12, 14, 18-20). Also, lower self-efficacy with respect to fatigue (11, 14, 18), a perceived lack of social support (11, 18), lower mental health (17), coping strategies like worrying and resting, catastrophising of fatigue, low self-esteem, strong somatic fatigue attributions and less social functioning were related to higher fatigue in RA (14). Longitudinal studies assessing fatigue over a period of one year showed that pain, daily functioning, and psychological factors such as self-efficacy and coping strategies were related to fatigue severity in RA (3, 21, 22). Physical functioning also seems an important variable associated with fatigue in RA: several studies showed that fatigue was closely related to activity limitations (1, 14, 17, 22, 23). However, how these factors together may contribute to fatigue in RA has been studied only once. This study of Nicassio *et al*. (2012) evaluated a multidimensional model using path analysis and found that disease activity contribute to fatigue through mood disturbance and poor sleep quality and that both disease activity and mood disturbance retained direct relationships with fatigue (24). Other possible relevant factors associated with fatigue in RA that were not regarded in that study (24) were, physical functioning (3, 9-11, 14, 17, 22, 25, 26), and sense of control (11, 14, 18) with respect to fatigue. Therefore, the objective of this study was to develop and test a multidimensional model of factors that determine fatigue severity in RA. Developing such a model of fatigue might facilitate the development of an effective treatment strategy for fatigue in RA.

## Methods

### *Design*

In this study, multidimensional path analysis modeling was applied using cross-sectional data on fatigue, disease characteristics and psychosocial and behavioral outcomes in consecutive patients with established RA (14, 26). Approval for this study was obtained from the Medical Ethics Committee Arnhem-Nijmegen in the Netherlands and all participants provided written informed consent.

### *Recruitment of patients*

A total of 431 RA patients aged 18–75 years visiting their rheumatologist for a scheduled 3-monthly check up appointment at the outpatient clinic of the Radboud University Medical Centre were asked to participate between June 2006 and October 2007. Patients received written information about the study and were informed orally by their rheumatologist or nurse specialist. Inclusion criteria were: diagnosed with RA according to the 1987 ACR classification criteria, between 18 to 75 years of age and able to read and write Dutch. Patients were not included if they had a second rheumatic disease, a history of malignancies or other comorbidities associated with chronic fatigue or if they had a current diagnosis

of depression and/or current psychological or psychiatric treatment. Study participation was allowed with the following comorbidities (well controlled): regulated thyroid disease, a controlled diabetic mellitus, a mild non restrictive chronic obstructive pulmonary disease and a successfully treated not metastasised basal cell carcinoma or squamous cell carcinoma in the skin.

*Data collection*

Patient characteristics (gender, age, body mass index (BMI)), disease characteristics, (pain, disease duration, rheumatoid factor) and medication use were collected at inclusion by research nurses. Blood samples were taken to determine ESR, CRP and haemoglobin level, and disease activity was assessed by the rheumatologist or a specialised rheumatology nurse, by using the disease activity score (DAS28) (27, 28). Fatigue was collected at baseline using a patient questionnaire. The following psychosocial and behavioural variables that might influence fatigue were collected: mood disturbance, sense of control over fatigue, poor sleep quality and physical functioning, using a patient questionnaire.

*Fatigue*

Fatigue severity was measured using the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS20) (29). The CIS-fatigue consists of 8 items and all items are scored on a 7 point Likert-scale (range 8–56), asking about fatigue severity the last two weeks. Higher scores indicate a higher level of experienced fatigue. A score of ≥35 indicates severe fatigue. The CIS fatigue severity subscale has proven to be a reliable and valid instrument in numerous conditions and was also used in RA (14, 29). The internal consistency of the CIS-fatigue severity subscale by Cronbach's alpha was 0.88 (29). Fatigue was also assessed using the vitality scale of the SF-36 consisting of four questions about vitality and fatigue with a range between 0–100, where higher scores indicate a higher level of vitality which is regarded as a lower level of fatigue. Cronbach's alpha was 0.74 (30).

*Pain*

Pain severity was assessed using the Bodily Pain subscale of the Short Form Health Survey (SF-36-BP) and a visual analogue scale (VAS) assessing current pain severity (range 0 (no pain) to 100 (violent pain)). The SF-36-BP asks about pain and interference by pain during the last four weeks (31), (range 0–100) with higher scores indicating less pain. Cronbach's alpha was 0.86 (30).

*Physical functioning*

Physical functioning was assessed using the SF-36 subscales physical functioning and role functioning (31). The total score ranges between 0-100 with higher scores indicating better physical functioning or role functioning. Cronbach's alpha of SF-36 subscale physical functioning and role functioning were 0.90 and 0.78, respectively (30).

*Mood disturbance*

Self reported depressive symptoms were assessed with 16 statements of the Symptom Check List 90 (SCL90) (32). The SCL depression consists of a 5-point likert scale ranges between 16–80. Higher scores indicate the presence of more (severe) depressive symptoms. Cronbach's alpha was 0.91 (32).

Anxiety was assessed with 10 statements of the Symptom Check List 90 (SCL90) (32). The SCL anxiety consists of a 5-point likert scale ranges between 10–50. Higher scores indicate more (severe) anxiety. Cronbach's alpha was 0.87 (32).

*Sense of control*

Sense of control about fatigue was assessed using the Self-Efficacy Scale 28 (SES28), a 7-item questionnaire scored on a 4-point Likert Scale (33) ranges between 7–28. Higher scores on the SES indicate more self-efficacy. Cronbach's alpha ranges between 0.68 and 0.77 (34, 35).

Helplessness of fatigue was assessed with the subscale helplessness of the Fatigue Catastrophising Scale (FCS). The FCS is the same questionnaire as the Pain Catastrophising Scale (36), in which the word pain is replaced by fatigue. Higher score on the scale indicates a higher tendency to be helplessness in response to fatigue. The Cronbach's alpha of the FCS helplessness tested in our study sample was 0.85.

*Sleep quality*

Poor sleep quality was assessed by the subscale sleep disturbance (3 items) of the Symptom Check List 90 (SCL90) (32). The SCL90 consists of a 5-point Likert scale. Total score ranges between 3–15 with higher scores indicating more sleep problems. Cronbach's alpha was 0.80 (32).

*Statistical analyses*

To test for differences between non severely fatigued patients (CIS-fatigue <35) and severely fatigued patients (CIS-fatigue ≥35) (based on Vercoulen (29)), a chi-square test, unpaired *t*-test or a Mann-Whitney U-test was used as appropriate (Table I).

Structural equation modelling (SEM) is a statistical technique for testing hypothesised patterns of directional and non-directional relationships ('path analysis') among a set of observed (measured) and unobserved (latent) variables. First the model of Nicassio (24) was tested in our data of RA patients. This model included constructs of disease activity, mood disturbance, sleep quality and fatigue (Fig. 1). The model was assessed using multiple fit criteria: the comparative fit index (CFI), the standardised root mean residual (SRMR) and the root mean square error of approximation (RMSEA). The criteria of an SRMR <0.09 and a RMSEA <0.06 is considered optimal to minimise the rates of type I and type II error (37, 38). The RMSEA is a measure of the degree to which the model holds in larger samples. Values up to 0.05 indicate a close fit in larger populations. A CFI value of >0.90 is an indication of a good fitting model (38). The explained variance of the latent variable fatigue was analysed by the R squared measure of goodness of fit.

After testing the model of Nicassio (24) in our data, a hypothesised model for fatigue was further developed (Fig. 2). This hypothesised model was based on the model of Nicassio *et al*. in which pain (as a measure of disease activity), mood and poor sleep quality are relevant (24) and the model of the chronic

**Table I.** Baseline characteristics of all included variables.

| | Variables | All patients (n=228) | CIS-fatigue <35 at baseline (n=132) | CIS-fatigue ≥35 at baseline (n=96) | *p*-value |
|---|---|---|---|---|---|
| Patient characteristics | Age | 55.9 (10.8) | 58.06 (10.0) | 52.95 (11.21) | <0.001 |
| | Gender,♀ (%) | 63 | 58 | 70 | 0.08 |
| | BMI | 25.5 (23.3-27.9) | 25.7 (23.1 – 27.8) | 25.3 (23.4 -28.4) | 0.73 |
| Medication use | DMARD monotherapy (%) | 63.6 | 68.2 | 57.3 | 0.09 |
| | MTX monotherapy (%) | 36.4 | 39.4 | 32.3 | 0.27 |
| | DMARDs ≥2 (%) | 13.2 | 13.7 | 12.5 | 0.80 |
| | Biological use (%) | 35.5 | 34.8 | 36.5 | 0.80 |
| | Oral prednisone (%) | 13.2 | 12.9 | 13.5 | 0.88 |
| Disease related variables | Rheumatoid factor, + (%) | 74.9 | 82 | 66 | 0.02 |
| | Illness duration, years | 11 (6-17) | 11 (7-17) | 10 (5-17) | 0.15 |
| | DAS 28 (0-10) | 3.2 (1.3) | 2.9 (1.8) | 3.7 (1.3) | <0.001 |
| | SJC 28 (0-28) | 4 (2-7) | 3 (1-6) | 4 (2-8) | 0.009 |
| | TJC 28 (0-28) | 2 (0-4) | 1 (1-3) | 3 (1-6) | <0.001 |
| | VAS GH (0-100) | 31.8 (21.5) | 24.4 (16.9) | 41.9 (23.0) | <0.001 |
| | ESR, mm/h | 8 (4-17) | 9 (4-19) | 7 (4-16) | 0.89 |
| | CRP, mg/l † | 0 (0-8) | 0 (0-6) | 0 (0-11) | 0.04 |
| | Haemoglobin, mmol/l | 8.2 (0.70) | 8.2 (0.7) | 8.2 (0.7) | 0.60 |
| Fatigue | CIS-fatigue baseline (8-56) | 31.5 (12.8) | 22.4 (7.7) | 44.1 (6.1) | <0.001 |
| | SF-36 vitality (0-100) | 56.8 (20.2) | 68.0 (14.4) | 41.4 (16.6) | <0.001 |
| Pain | VAS pain severity (0-100) | 31.1 (21.9) | 24.8 (18.1) | 39.7 (23.8) | <0.001 |
| | SF-36 bodily pain (0-100)‡ | 64.2 (19.8) | 72.7 (16.9) | 52.5 (17.6) | <0.001 |
| Physical functioning | SF-36 physical functioning (0-100)‡ | 59.6 (24.4) | 69.1 (21.8) | 46.6 (21.7) | <0.001 |
| | SF-36 role functioning (0-100)‡ | 45.39 (40.31) | 62.31 (38.4) | 22.14 (30.1) | <0.001 |
| Mood disturbance | SCL 90 depressive thoughts (16-80) | 21 (17-24) | 18 (17-21.8) | 23 (20-28.8) | <0.001 |
| | SCL 90 anxiety (10-50) | 11 (10-14) | 10.5 (10-13) | 13 (11-15.8) | <0.001 |
| Sense of control | SES 28 (7-28) | 19.5 (3.5) | 20.6 (3.1) | 18.3 (3.5) | <0.001 |
| | FCS-helplessness (0-24) | 3 (0.3-6) | 2 (0-5) | 4 (1-8) | <0.001 |
| Sleep quality | SCL90 sleep quality (3-15) | 5 (3.3-8) | 5 (3-6) | 7 (4-9.8) | <0.001 |

Numbers are mean (SD); Median (P25-P75) or n (%) as denoted. ‡ scored on a reversed scale, a higher score means better functioning and less pain. DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; DAS28: Disease Activity Score of 28 joints; SJC28: Swollen joint count of 28 joints; TJC28: Tender joint count of 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; CIS-fatigue: Checklist Individual Strength of Fatigue; SF-36: Short Form Health Survey 36; SCL-90: Symptom Check List 90; SES: Self Efficacy Scale; FCS: Fatigue Catastrophising Scale.

fatigue syndrome of Vercoulen *et al*. in which sense of control is an important factor. Thereby our previous study showed that physical functioning is related to RA fatigue, more active RA patients showed less fatigue than passive RA patients (39). We therefore included these variables for RA fatigue in our hypothesised model; which accordingly included constructs of pain, physical functioning, mood, sense of control, sleep quality and fatigue. We included VAS pain and SF-36 bodily pain as indicators for the latent variable pain. Physical functioning was included as a latent variable in the model with 2 indicators representing SF-36 physical functioning and SF-36 role functioning. Mood disturbance was included as a latent variable with 2 indicators representing depressive thoughts (SCL90 depression) and anxiety (SCL90 anxiety). Sense of control was included as a latent variable with 2 indicators representing helplessness (FCS-helplessness) and self-efficacy (SES28). Poor sleep quality was included as a latent variable with 1 indicator representing SCL90 sleep quality. Finally, fatigue was included as the latent variable in the model with 2 indicators representing the CIS fatigue and the SF-36 vitality (Fig. 2).

Analyses were performed using SPSS 20.0 and MPlus (v. 6.0).

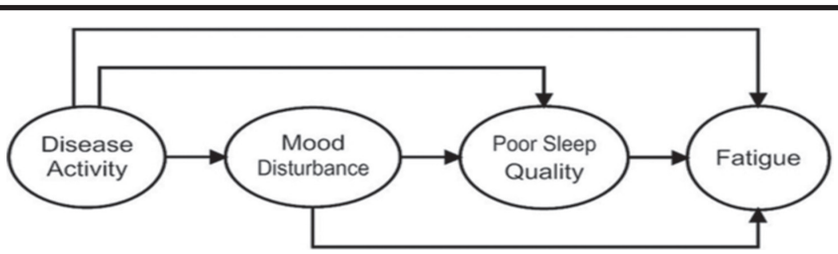


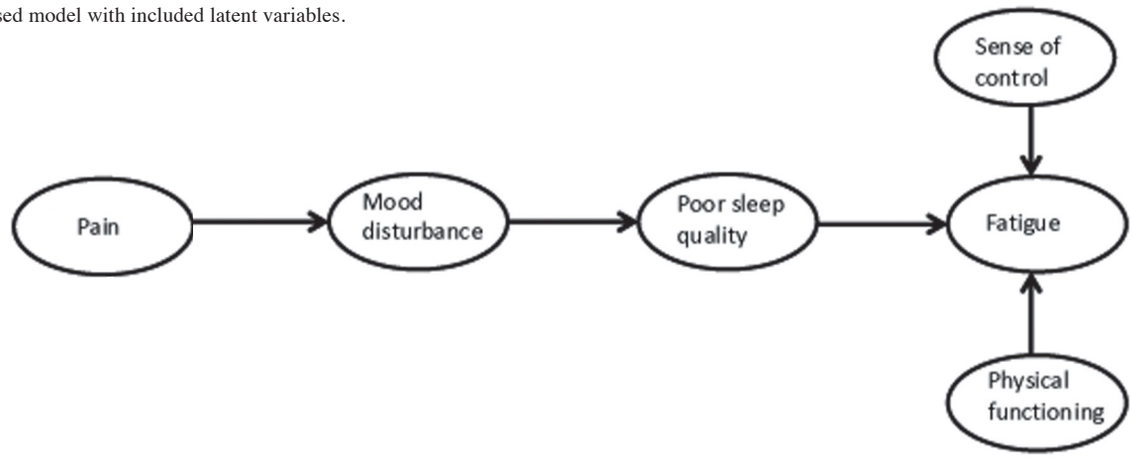

**Fig. 1.** A multidimensional model of fatigue in patients with rheumatoid arthritis. Reproduced from the Journal of Rheumatology with permisson. NICASSIO P.M. *et al*.: *J Rheumatol* 2012; 39: 1807-13.

## Results

A total of 230 patients were included. Two patients were excluded after the measurements because of a sleep apnoea and a malignant lung tumour, thus 228 patients were included in the analyses (Table I).

The mean age was 55.9 years, 63% was female and overall the majority had a

**Fig. 2.** Our hypothesised model with included latent variables.




low disease activity and a moderate fatigue level (29). At baseline, 36% received a tumour necrosis factor-inhibiting agent, either as monotherapy or in combination with a DMARD. Most disease related and other variables, including pain, physical functioning, mood disturbance, sense of control and sleep quality were all significantly different between severely fatigued patients and non severely fatigued patients at baseline (Table I).

*Model for fatigue*

All data were screened for normality and there were no outliers. Testing the model of Nicassio *et al*. in our data resulted in a low model fit: a CFI of 0.82; RMSEA was 0.193 and SRMR was 0.166. This indicates that this model does not fit well in our data.

Next we tested our hypothesised model which revealed an indirect path from pain to fatigue through mood disturbance and poor sleep quality. Both sense of control and physical activity retained direct relationships with fatigue. The fit (CFI) of the hypothesised model was 0.936, RMSEA=0.095 and SRMR=0.084.

The modification indices of the SEM test indicated that an extra path from sense of control to mood disturbance would have a significant positive effect on the model fit. There was also a significant positive effect of pain on physical functioning. The path from pain to mood disturbance and the path from sense of control to fatigue were not significant and were removed. Thereby an extra path from sense of control to pain and a direct path to physical functioning would gave a better fit. Finally, the revised final model provided a better fit to the data. Figure 3 showed the final model with standardised correlation coefficients and Table II the unstandardised and standardised coefficients between the latent variables of the final model. The CFI of the final model was 0.976; RMSEA was 0.058 and SRMR was 0.043. Results of figure 3 and table 2 show that poor sleep quality (β=0.42, $p$<0.001) and less physical functioning (β=-0.65, $p$<0.001) are related to a higher level of fatigue in RA. Thereby, less sense of control (more helplessness and less self-efficacy) is related to more mood disturbance (β=-0.64, $p$<0.001). More mood disturbance is related to poor sleep quality (β=0.78, $p$<0.001) which is related to a higher level of fatigue. In addition, a higher pain level

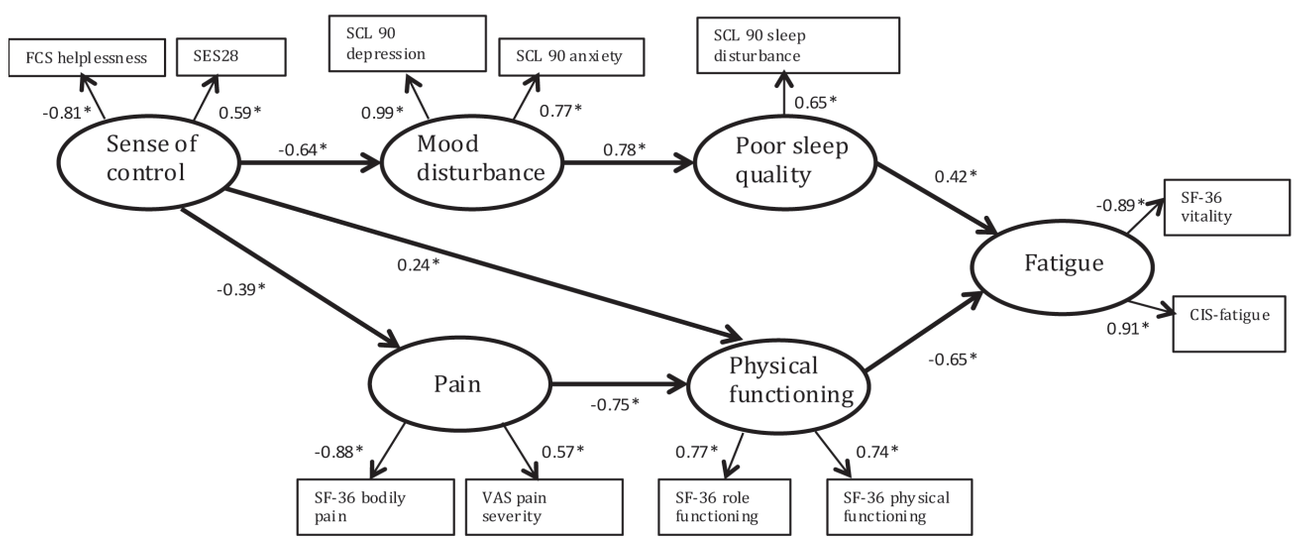



**Fig. 3.** The final model with standardised correlation coefficients. SF-36: Short Form Health Survey 36, SCL-90: Symptom Check List 90. VAS: visual analogue scale, CIS: Checklist Individual Strength. * $p$<0.001. The latent variables are shown in rounds and the constructs of the latent variables are shown in squares.

**Table II.** Path coefficients of the final structural equation model. Unstandardised means that the coefficients are uncorrected for differences in scaling. SE: standard error. Standardised means that the coefficients are corrected for scale differences to facilitate comparison.

| Effects | Unstandardised | SE | *p*-value | Standardised |
|---|---|---|---|---|
| Poor sleep quality → fatigue | 3.881 | 0.789 | <0.001 | 0.419 |
| Physical functioning → fatigue | -0.641 | 0.076 | <0.001 | -0.648 |
| Pain → physical functioning | -1.087 | 0.168 | <0.001 | -0.752 |
| Sense of control → mood disturbance | -1.249 | 0.162 | <0.001 | -0.638 |
| Mood disturbance → poor sleep quality | 0.220 | 0.028 | <0.001 | 0.781 |
| Sense of control → physical functioning | 1.244 | 0.442 | <0.001 | 0.241 |
| Sense of control → pain | -1.391 | 0.367 | <0.001 | -0.389 |

is related to less physical functioning (β=-0.75, $p$<0.001) which is related to a higher fatigue level. Thereby less sense of control is related to more pain (β=0.39, $p$<0.001) and less physical functioning (β=-0.24, $p$<0.001) The R square was 0.74 which means that the model explained 74% of the variance in fatigue in RA.

## Discussion

According to the multidimensional path analysis model developed in this study, RA fatigue is influenced directly by poor sleep quality and physical functioning, and indirectly by sense of control, mood disturbance, poor sleep quality and pain. This means that poor sleep quality and a lower physical functioning are directly associated with a higher fatigue level. Indirectly, more pain was associated with less physical functioning; more mood disturbance was associated with poor sleep quality, and less sense of control was associated with more mood disturbance, more pain and less physical functioning. The model explained about three quarters of the variance in fatigue in RA.

A multidimensional model of fatigue for patients with RA was tested in only one other study (24). According to that model, higher levels of disease activity, mood disturbance and poor sleep quality had direct and indirect effects on fatigue, explaining 62% of the variance in fatigue (24). However this model did not fit well in our sample of RA patients, although it is clear that models generally perform somewhat worse in external data. Nevertheless, we tried to make a better fitting model with inclusion of psychosocial factors and physical functioning besides pain, mood disturbance and sleep quality. Notably, another explanation for the relatively poor fit of Nicassio's model in our RA sample could be the different use of measurement instruments, besides sample differences. The model we developed explained 74% of the variance in fatigue, which is quite well.

In several studies it has been analysed which disease-related and/or psychosocial variables are associated with fatigue (3, 13, 21, 22). These studies provided evidence that disability (3, 22), lower self-efficacy (21), sleep disruption and depressed mood (21), and more trait anxiety (22) were associated with future fatigue in RA. A recent systematic review concerning factors related to fatigue in RA, concluded that three variables have a high probability to be involved in the complex process of fatigue in RA: pain, disability and depressive mood, while more evidence was found for fatigue being related to pain and physical function than to depression (13). The factors in the model of our study are in line with this review. Our findings suggest that fatigue in RA is directly associated with physical functioning and poor sleep quality and indirectly by pain, sense of control and mood disturbance.

A limitation of our study is that using SEM in a cross-sectional design no definitive cause-effect relationship can be determined. Cause-effect relations can best be studied using a randomised controlled trial or a longitudinal design. Another limitation is the total number of patients included, which limits the number of variables that can be included in the model. As measures of physical function we used patient questionnaires: SF-36 physical functioning and SF-36 role functioning, which were also used in the previous studies. Patient questionnaires represent perceived activity, rather than objectively measured activity. However, inclusion of objectively assessed actometer scores that were available in a large subset of the patients did not change the model nor the model fit (data not shown). Another limitation is that we could not validate our model because of the sample size. To validate our treatment model and to facilitate generalisation, it should be tested in another sample of RA patients.

Developing a model of fatigue might facilitate the development of a treatment strategy for fatigue in RA. The five factors: pain, mood disturbance, sense of control, sleep quality and physical functioning, found in our study are perpetuating factors of fatigue and this is interesting for fatigue treatment. If these factors could effectively be treated, this may lead to improvement in patients' fatigue. Pain in RA is treated with antirheumatic medication and pain-medication (40, 41). However, pain treatment alone is insufficient to treat fatigue as fatigue frequently occurs in patients with low or moderate disease activity (3).

Psychological interventions, notably CBT, can be used for improving sense of control and mood and as consequence a better sleep quality. Studies of Hewlett and Evers indicated that CBT improves fatigue impact, coping and perceived severity and well-being in RA (5, 42). Stimulus control instructions, and sleep restriction have proven to be effective in other sleep-disordered populations (43, 44).

Little has been reported on the effectiveness of CBT in reducing sleep disturbances in patients with RA (45) although a study found improvements in subjective sleep quality after CBT (46). A recent yet incompleted trial is investigating the effect of intermittent aerobic exercise on the improvement of sleep in patients with rheumatoid arthritis (47), however the effect is not known yet.

Alternatively, an exercise programme to increase the level of physical activity (functioning) could be effective in reducing fatigue. Several RCTs and a meta-analysis provided evidence that several types of physical activity provide benefit for fatigue in adults with RA (4).

In summary, according to our model, RA fatigue is influenced by pain, sleep

quality, sense of control, mood and physical functioning. This suggests that treatments aimed at these five factors could help to reduce fatigue in RA. Treatment studies, especially RCTs, are needed to test the efficacy of these interventions.

## References


1. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.
2. HEWLETT S, CHALDER T, CHOY E *et al*.: Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology* (Oxford) 2011; 50: 1004-6.
3. REPPING-WUTS H, FRANSEN J, VAN ACHTERBERG T, BLEIJENBERG G, VAN RIEL P: Persistent severe fatigue in patients with rheumatoid arthritis. *J Clin Nurs* 2007; 16: 377-383.
4. CRAMP F, HEWLETT S, ALMEIDA C *et al*.: Non-pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2013; 8: CD008322.
5. HEWLETT S, AMBLER N, ALMEIDA C *et al*.: Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Ann Rheum Dis* 2011; 70: 1060-7.
6. DIXON KE, KEEFE FJ, SCIPIO CD, PERRI LM, ABERNETHY AP: Psychological interventions for arthritis pain management in adults: a meta-analysis. *Health Psychol* 2007; 26: 241-50.
7. DICKENS C, MCGOWAN L, CLARK-CARTER D, CREED F: Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med* 2002; 64: 52-60.
8. SINGH H, ARYA S, TALAPATRA P *et al*.: Assessment of fatigue in rheumatoid arthritis (by Functional Assessment of Chronic Illness Therapy-Fatigue score) and its relation to disease activity and anemia. *J Clin Rheumatol* 2014; 20: 87-90.
9. CAMPBELL RC, BATLEY M, HAMMOND A, IBRAHIM F, KINGSLEY G, SCOTT DL: The impact of disease activity, pain, disability and treatments on fatigue in established rheumatoid arthritis. *Clin Rheumatol* 2012; 31: 717-22.
10. GARIP Y, ESER F, AKTEKIN LA, BODUR H: Fatigue in rheumatoid arthritis: association with severity of pain, disease activity and functional status. *Acta Reumatol Port* 2011; 36: 364-9.
11. HUYSER BA, PARKER JC, THORESON R, SMARR KL, JOHNSON JC, HOFFMAN R: Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 2230-7.
12. POLLARD LC, CHOY EH, GONZALEZ J, KHOSHABA B, SCOTT DL: Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* (Oxford) 2006; 45: 885-9.
13. NIKOLAUS S, BODE C, TAAL E, VAN DE LAAR MA: Fatigue and factors related to fatigue in rheumatoid arthritis: A systematic review. *Arthritis Care Res* (Hoboken) 2013.
14. VAN HOOGMOED D, FRANSEN J, BLEIJENBERG G, VAN RIEL P: Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology* (Oxford) 2010; 49: 1294-302.
15. CROSBY LJ: Factors which contribute to fatigue associated with rheumatoid arthritis. *J Adv Nurs* 1991; 16: 974-81.
16. BELZA BL: Comparison of self-reported fatigue in rheumatoid arthritis and controls. *J Rheumatol* 1995; 22: 639-43.
17. THYBERG I, DAHLSTROM O, THYBERG M: Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. *J Rehabil Med* 2009; 41: 904-12.
18. RIEMSMA RP, RASKER JJ, TAAL E, GRIEP EN, WOUTERS JM, WIEGMAN O: Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. *Br J Rheumatol* 1998; 37: 1042-6.
19. TACK BB: Fatigue in rheumatoid arthritis. Conditions, strategies, and consequences. *Arthritis Care Res* 1990; 3: 65-70.
20. WOLFE F, MICHAUD K: Predicting depression in rheumatoid arthritis: the signal importance of pain extent and fatigue, and comorbidity. *Arthritis Rheum* 2009; 61: 667-73.
21. TREHARNE GJ, LYONS AC, HALE ED, GOODCHILD CE, BOOTH DA, KITAS GD: Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychol Health Med* 2008; 13: 494-504.
22. MANCUSO CA, RINCON M, SAYLES W, PAGET SA: Psychosocial variables and fatigue: a longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. *J Rheumatol* 2006; 33: 1496-502.
23. LEE EO, KIM JI, DAVIS AH, KIM I: Effects of regular exercise on pain, fatigue, and disability in patients with rheumatoid arthritis. *Fam Community Health* 2006; 29: 320-7.
24. NICASSIO PM, ORMSETH SR, CUSTODIO MK, IRWIN MR, OLMSTEAD R, WEISMAN MH: A multidimensional model of fatigue in patients with rheumatoid arthritis. *J Rheumatol* 2012; 39: 1807-13.
25. NEUBERGER GB, AARONSON LS, GAJEWSKI B *et al*.: Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 943-52.
26. VAN DARTEL SA, REPPING-WUTS JW, VAN HOOGMOED D, BLEIJENBERG G, VAN RIEL PL, FRANSEN J: Association between fatigue and pain in rheumatoid arthritis: does pain precede fatigue or does fatigue precede pain? *Arthritis Care Res* (Hoboken) 2013; 65: 862-9.
27. VAN RIEL PL: The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S-65-74.
28. SCOTT IC, SCOTT DL: Joint counts in inflammatory arthritis. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S-7-12.
29. VERCOULEN JH, SWANINK CM, FENNIS JF, GALAMA JM, VAN DER MEER JW, BLEIJENBERG G: Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994; 38: 383-92.
30. BUCHWALD D, PEARLMAN T, UMALI J, SCHMALING K, KATON W: Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals. *Am J Med* 1996; 101: 364-70.
31. AARONSON NK, MULLER M, COHEN PD *et al*.: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998; 51: 1055-68.
32. ARRINDELL WA: Dimensional structure, reliability and validity of the Dutch version of the Symptom Checklist (SCl-90): data based on a phobic and "normal" population. *Ned Tijdschr Psychol* 1991; 36: 77-108.
33. BLEIJENBERG G, BAZELMANS E, PRINS J: Chronisch vermoeidheidssyndroom (praktijkreeks gedragstherapie): Houten/Diegem: *Bohn Stafleu Van Loghum*; 2001.
34. WIBORG JF, KNOOP H, FRANK LE, BLEIJENBERG G: Towards an evidence-based treatment model for cognitive behavioral interventions focusing on chronic fatigue syndrome. *J Psychosom Res* 2012; 72: 399-404.
35. B DE VREE SVDW, J PRINS, E BAZELMANS, J VERCOULEN, P SERVAES: Meetinstrumenten bij chronische vermoeidheid 2002; 35: 157-64.
36. VAN DAMME S, CROMBEZ G, BIJTTEBIER P, GOUBERT L, VAN HOUDENHOVE B: A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain* 2002; 96: 319-24.
37. BENTLER PM, DUDGEON P: Covariance structure analysis: statistical practice, theory, and directions. *Annu Rev Psychol* 1996; 47: 563-92.
38. BENTLER PM: Comparative fit indexes in structural models. *Psychol Bull* 1990; 107: 238-46.
39. RONGEN-VAN DARTEL SA, REPPING-WUTS H, VAN HOOGMOED D *et al*.: Relationship between objectively assessed physical activity and fatigue in patients with rheumatoid arthritis: inverse correlation of activity and fatigue. *Arthritis Care Res* (Hoboken) 2014; 66: 852-60.
40. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
41. HETLAND ML, JENSEN DV, KROGH NS: Monitoring patients with rheumatoid arthritis in routine care: experiences from a treat-to-target strategy using the DANBIO registry. *Clin Exp Rheumatol* 2014; 32 (Suppl. 85): S-141-146.
42. EVERS AW, KRAAIMAAT FW, VAN RIEL PL, DE JONG AJ: Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 2002; 100: 141-53.
43. MORIN CM, CULBERT JP, SCHWARTZ SM: Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 1994; 151: 1172-80.
44. IRWIN MR, COLE JC, NICASSIO PM: Comparative meta-analysis of behavioral interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+ years of age. *Health Psychol* 2006; 25: 3-14.
45. BOURGUIGNON C: Investigating sleep disturbances in adults with rheumatoid arthritis. *holist nurs pract* 2003; 17: 241-9.
46. O'LEARY A, SHOOR S, LORIG K, HOLMAN HR: A cognitive-behavioral treatment for rheumatoid arthritis. *Health Psychol* 1988; 7: 527-44.
47. LOPPENTHIN K, ESBENSEN BA, JENNUM P *et al*.: Effect of intermittent aerobic exercise on sleep quality and sleep disturbances in patients with rheumatoid arthritis - design of a randomized controlled trial. *BMC Musculoskelet Disord* 2014; 15: 49.