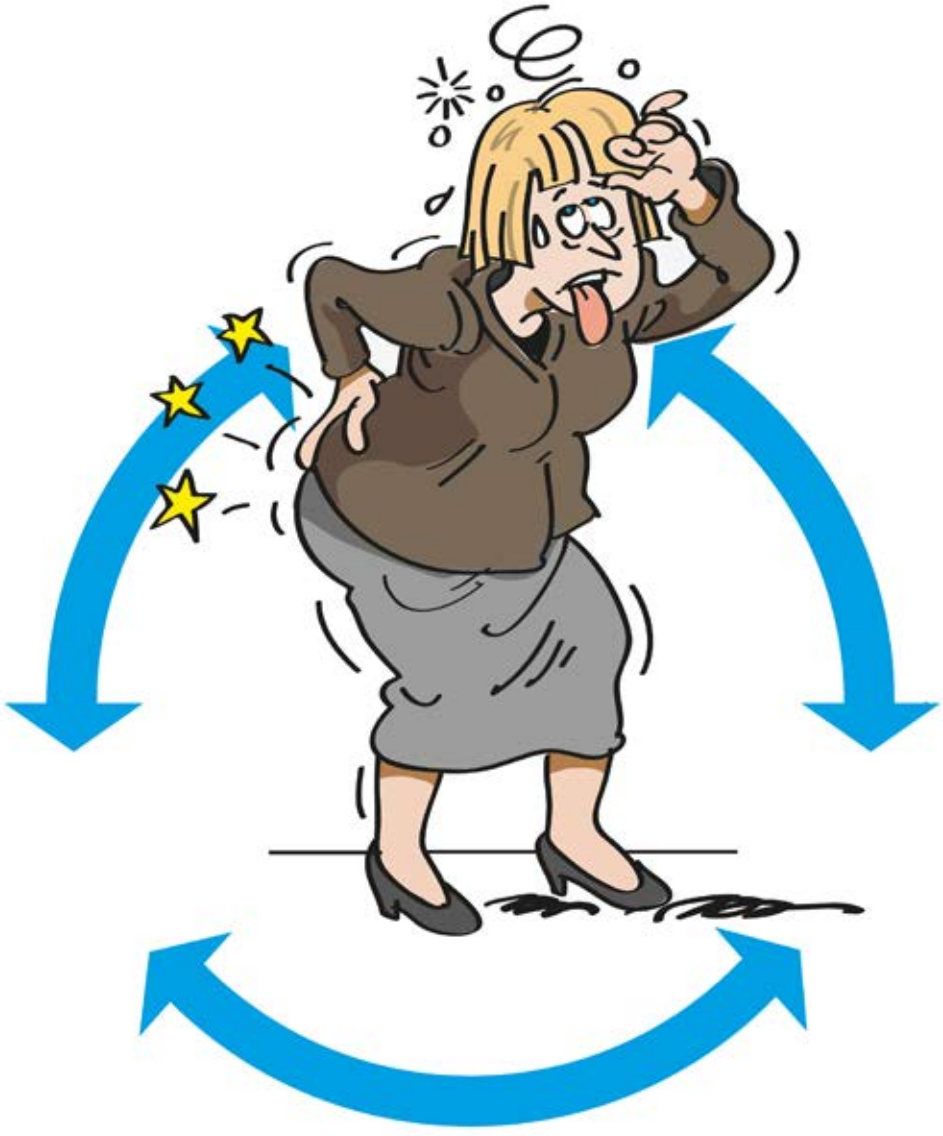
# Physical activity and fatigue in rheumatoid arthritis: a vicious circle?



Sanne Rongen-van Dartel

# Physical activity and fatigue in rheumatoid arthritis: a vicious circle?

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**Colofon**

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# Physical activity and fatigue in rheumatoid arthritis: a vicious circle?

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## Table of contents

# Chapter 1

## General introduction

## Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic inflammatory disease, characterized by synovitis of multiple joints, resulting in pain, disability, and progressive joint destruction (1). Patients with RA have a higher mortality rate compared to the general population (2). RA affects about 0.5-1% of the population world-wide and occurs more frequent in woman (1, 3). In the Netherlands about 116.000 people were diagnosed with RA in 2011, of which 74.000 were female and 42.000 were male (4). Although the disease can occur at any age, its incidence increases with age and most cases have an onset between 40 and 70 years (5).

The precise etiology of RA is unknown. The pathogenesis is multifactorial, and both genetic factors, environmental factors and immunological factors play a role (5-7). So far there is no therapy available to cure the disease. Pharmacological treatment with so called Disease Modifying Antirheumatic Drugs (DMARD), such as methotrexate, and Biological Response Modifiers, such as anti-tumor necrosis factor (anti-TNF), is available to reduce and control the disease activity, and to prevent the destruction of synovial joints. Non-pharmacological treatments, such as physical therapy and psychological counseling, are aimed to control symptoms and improve daily functioning in patients with RA.

## Fatigue as a symptom

Symptoms that are frequently reported by patients with RA are joint pain, joint stiffness, impairment in daily functioning, and fatigue (8-11). Pain as well as fatigue were mentioned by patients with RA as being the two most disturbing symptoms of the disease (12-15). It seems that since the disease activity in RA is better controlled due to more effective treatment options, feeling less fatigued is more important for patients with RA than improving other outcomes such as joint swelling and stiffness (14).

The importance and recognition of fatigue as patient relevant symptom has grown. Nevertheless, fatigue is not yet included in the ACR core set variables used to assess the efficacy of potential DMARDs in trials (16). However, the patient perspective workshop at OMERACT 8 (an international group of experts on Outcome Measures in Rheumatology Clinical Trials) endorsed the proposal that, in addition to the “core set” of outcome measures currently in widespread use, fatigue should be measured in future studies of RA whenever possible (17). The workshop concluded that fatigue is a symptom that is important to patients, is commonly reported by patients, is often severe, is responsive to some interventions, can be measured by several current instruments, and provides information additional to that commonly obtained from currently used outcomes (17). Unfortunately, fatigue in RA is not mild and it tends to stay. Already in 2007 Rep-

ping-Wuts showed that in RA fatigue is often severe as well as persistent; 40% of the patients with RA were severely fatigued at baseline and after one year (18). Other longitudinal studies did also show that fatigue is relative stable over time, although fatigue was only measured at baseline and at 12 months, not in the intermediate period (19, 20).

Fatigue is not a negative symptom per se. But, patients with RA experience fatigue differently than healthy people do experience fatigue (10, 21). The kind of fatigue healthy people experience may for example result from strenuous physical exercising or a busy week. This is normal fatigue and resting brings relief. However this is not the case in patients with RA where patients express their fatigue as exhaustive, debilitating and restricting daily functioning (10, 21-23). Moreover, fatigue causes changes in cognitive ability and overall activity pattern and an increased need for sleep and rest causes an imbalance in daily life (23).

Fatigue in RA is variable in duration and intensity and not occurring at regular times or same days of the week (21). In addition, Repping-Wuts showed that fatigue has a greater impact on daily life than pain has (21). However, patients with RA seldom mentioned fatigue explicitly to their professional healthcare providers, assuming that it cannot be treated and that they must manage it alone (21). Although it appears that fatigue is severe and prevalent in RA, in the general population fatigue appears not to be uncommon, at least in the Western society. Whether fatigue in RA indeed is more severe than in the general population is not clear. In RA fatigue, many factors may play a role, however it is unknown which factors are either cause or consequence of fatigue in RA. Different cross-sectional studies have been performed when investigating associations between different factors and fatigue in RA. A causal relationship between these variables and fatigue in RA is difficult to establish, and needs testing in longitudinal observational studies or RCT's with interventions for these factors. However, to increase evidence how these factors together may contribute to fatigue in RA, a multidimensional 'path analysis' model could be devised and this will give knowledge which factors should be treated to reduce fatigue in RA.

## Treatment of fatigue

Currently there is no clearly effective treatment strategy available to treat fatigue in RA. The lack of knowledge of effective interventions has led to fatigue being neglected during patient-physician contacts (24, 25). The presence of fatigue in patients with RA who are reasonably well treated for their RA, suggests that DMARD and biological treatment may not be sufficient to treat RA fatigue. That is to say, there is some evidence that in RA, pharmacological treatments indeed reduce fatigue, together with pain and disease activity, but generally speaking, fatigue is unresolved. The largest reductions in fatigue occurred during the first

6 months of treatment and effect sizes were modest (26-29). In a quasi-experimental study of patients with established RA, it appeared that there was no difference in persistent severe fatigue between users of DMARDs and anti-TNF users (30).

In patients with other chronic disorders in which fatigue is a long-term symptom, such as cancer survivors and patients with the chronic fatigue syndrome (CFS), cognitive behavioural therapy (CBT) is effective in treating fatigue (31-33). In patients with CFS, besides CBT, graded exercise therapy (GET) also is effective in treating fatigue (34, 35). CFS is notoriously difficult to treat, and it appears that CBT and GET level are the only effective interventions. Therefore, there is a good reason to regard CBT and increasing physical activity as two likely candidates to treat fatigue in RA.

## Physical activity as a treatment option for fatigue

RA affects one's movement apparatus, and consequently may cause disability and impair one's level of physical activity. That patients with RA experience excess disability, beyond the influence of age and gender is already clear. Indeed, decreased levels of self-reported physical activity have been reported among patients with RA (36-38), however physical activity in RA has not been measured objectively.

It is assumed that physical activity is decreased in patients with RA as a consequence of fatigue, joint pain, restricted mobility, reduced muscle mass, less strength and aerobic capacity (39-41). This also implies that reduced physical activity can be a cause as well as a consequence of fatigue in RA. Factors most strongly related to inactivity in RA were reduced self-efficacy for exercise (42), fear avoidance (43), lack of strong motivation for physical activity and lack of strong beliefs related to physical activity (44, 45). In turn, physical inactivity in RA may lead to more severe fatigue, lower functional capacity, less quality of life and further progression of the disease (46-48). The persistence of fatigue may be related to the presence of some, roughly drawn, vicious circle (Figure 1).

Accordingly, it can be hypothesized that a decrease in physical activity is associated with a higher level of fatigue which leads to more mood disturbance and less sense of control associated with a further decrease in physical activity. In patients with other chronic conditions such as CFS, Sjögren's syndrome, cancer and Parkinson's disease, a higher level of fatigue seems associated with a lower level of physical activity (49-52). However, the relation between the level of physical activity and fatigue in RA is unknown yet. Increasing physical activity in patients with RA, could break this vicious circle and could have positive effects on fatigue with as consequence a better mood and more sense of control.

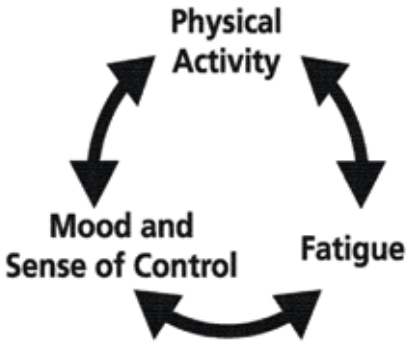


**Figure 1.** Hypothetical vicious circle

## Aim of this thesis

The aim of this thesis is to gain more insight into factors associated with fatigue in RA, especially the association between physical activity and fatigue. Clarifying the association between the level of physical activity and the level of fatigue may provide new knowledge if increasing the level of physical activity could break the vicious circle, fatigued patients with RA find themselves into.

## Outline of this thesis

In **chapter 1** an introduction to the problem of fatigue in RA is given and our hypothesis about the relationship between physical activity and fatigue is discussed. In **chapter 2** the course of fatigue and pain in patients with RA in a period of one year was investigated. The objective of this longitudinal study was to investigate whether changes in pain precede changes in fatigue, or vice versa, or whether pain and fatigue fluctuate together in time. In **chapter 3** it was investigated whether objectively measured activity levels and activity patterns are associated with fatigue levels in patients with RA, and whether pain, disability, coping, and/or cognition are associated with—or influence—the level of activity among patients with RA. The level of daily activity in patients with RA was investigated objectively during 14 consecutive days. In **chapter 4**, we compared the level of physical activity and the level of fatigue between patients with RA and the general Dutch population and investigated whether self-reported physical activity in RA depends on age, gender, BMI, and disease duration. In addition, it was described how many patients with RA are engaged in sports and in which sport activities. In **chapter 5**, a multidimensional model of factors that determine fatigue severity in RA was developed. Besides pain and physical functioning, other important factors related to fatigue in RA known from previous research were included, which are psychosocial factors, mood disturbance and sleep quality. Developing such a model of fatigue might facilitate which factors are meaningful targets for the treatment of fatigue in RA. In **chapter 6**, we performed a meta-analysis to summarize the limited evidence and estimated the mean effect of aerobic land-based exercise programs on fatigue in RA. In **chapter 7** we discuss our findings and recommendations for further research will be given. **Chapter 8** provides an overall summary.

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# Chapter 2

# The association between fatigue and pain in rheumatoid arthritis: Does pain precede fatigue or does fatigue precede pain?

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## Abstract

### Objective

Fatigue and pain are important symptoms for patients with Rheumatoid Arthritis (RA), but their temporal association is unknown. Therefore, the objective of this study was to investigate the longitudinal relation between fatigue and pain in patients with RA using time-lag models.

### Methods

Consecutive RA outpatients (N=228) were enrolled for this 1-year study. Fatigue was assessed monthly with the Checklist Individual Strength (CIS; range 8-56) and pain was assessed monthly with the Bodily Pain subscale (inverted, range 0-100) of the Short Form 36. The association between monthly changes in fatigue and pain was analyzed using longitudinal regression (mixed models), using the same months and with a 1-month time-lag.

### Results

A total of 198 patients were included in the analyses. At baseline, the mean ± SD pain score was 35.23 ± 19.82 and the mean ± SD CIS-fatigue score was 31.0 ± 12.4. Severe fatigue at baseline (CIS score ≥35) was present in 42% of the patients. The mean ± SD patient-averaged CIS-fatigue score over 1 year was 30.9 ± 6.0 and the mean ± SD patient-averaged pain score over 1 year was 36.4 ± 18.3. The longitudinal regression analysis showed a significant positive relationship between fatigue and pain during the same month (β=2.04, 95% confidence interval 1.82, 2.27). The models using a time lag showed no significant association between changes in pain and changes in fatigue.

### Conclusion

In established RA, pain and fatigue show monthly fluctuations that are synchronous rather than showing a temporal relation with a time-lag; within this time frame, the results do not indicate that one precedes the other.

## Introduction



Rheumatoid Arthritis (RA) is a chronic autoimmune disorder causing inflammation, stiffness and pain in the joints (1). In RA, fatigue is a frequently occurring and patient-relevant complaint which frequently is experienced as debilitating and restricting daily functioning (2). In cross-sectional studies, it is found that at least 40% of the RA patients is severely fatigued (3, 4). Pain and fatigue are the symptoms mentioned by RA patients as the most disturbing symptoms of the disease (5-7).

RA fatigue can be influenced by numerous factors, such as inflammation, pain, disability and psychosocial factors (mood, beliefs, behavior) (8-10). Although chronic inflammation might cause fatigue, in RA it has been shown that pain, rather than inflammation, is associated with fatigue severity (4, 7-9, 11-15). Fatigue and pain often co-occur, and there are previous mainly cross-sectional studies showing that more fatigue is strongly associated with more pain (4, 8, 9, 16). Few studies have measured fatigue over 1 year in RA (3, 15). It was shown that severe fatigue was experienced in 50% of the RA patients, both at baseline and at 12-month follow-up (3). Also in RA, a higher pain score at baseline predicted worse fatigue 1 year later (15).

The association of pain and fatigue could be synchronous or with a time lag, meaning that a change in pain could be associated with a change in fatigue at the same time (synchronous), or that a change in pain may precede a change in fatigue or a change in fatigue may precede a change in pain.

Temporal associations between pain and fatigue in RA might be day to day (e.g. pain today associated with fatigue tomorrow) or month to month (17-19). Currently, it is unclear whether a change in pain precedes a change in fatigue or whether a change in fatigue precedes a change in pain. It could be hypothesized both that pain can lead to fatigue because of the energy consumed by prolonged pain suppression and the need to deal with pain, but also that fatigue can lead to pain because of being less able to suppress and deal with pain (20, 21). Therefore, the question is whether increased levels of pain are followed by an increase in fatigue or whether it is vice versa: i.e., increased levels of fatigue are followed by an increase in pain. It also may be that changes in fatigue and pain tend to fluctuate together and do not show such a temporal association. Therefore, the objective of this study was to investigate the longitudinal relation between fatigue and pain in patients with RA using time-lag models.

## Patients and methods

### Design

This is a prospective cohort study of 1 year with monthly repeated measures of both fatigue and pain in consecutive patients with established RA. Over the course of 2 weeks, daily assessments of pain and fatigue were performed. Approval for this study was obtained from the ethical committee (CMO Arnhem-Nijmegen, The Netherlands).

### Patients

A total of 230 RA patients attending the outpatient clinic of the Radboud University Nijmegen Medical Centre were approached between June 2006 and October 2007 to participate in this study. Patients were informed in writing and orally by their rheumatologist or a nurse specialist and invited to participate in the study.

Inclusion criteria consisted of a diagnosis of RA according to the 1987 ACR classification criteria (22), being age 18–75 years, and being able to read and write in the Dutch language. Study participation was allowed with comorbidities such as secondary Sjögren's syndrome, regulated thyroid disease (values of free T4 of minimally 8 pmoles/liter and thyroid stimulating hormone, maximum 1.0 units/liter), regulated diabetes mellitus (normalized glucose values between 2.5 and 3.7 mmoles/liter in urine and between 4.0 and 5.6 mmoles/liter in blood and glycosylated hemoglobin <8.0%), mild nonrestrictive chronic obstructive pulmonary disease, and successfully treated not metastasized basal cell carcinoma or squamous cell carcinoma in the skin in medical history. Patients were excluded from study participation if they had a second rheumatic disease (except for secondary Sjögren's syndrome), a history of malignancies or other comorbidities associated with chronic fatigue, a current diagnosis of depression, or current psychological or psychiatric treatment.

### Data collection

Patient characteristics (sex and age), disease characteristics (disease duration and rheumatoid factor), and medication use were collected at inclusion (baseline) by research nurses. A blood sample was taken (for erythrocyte sedimentation rate, C-reactive protein level, and hemoglobin level) and disease activity was assessed by the rheumatologist or a research nurse using the Disease Activity Score in 28 joints (DAS28). Restrictions of daily functioning were assessed using the Health Assessment Questionnaire (HAQ) disability index (23).

Fatigue and pain were self-assessed every month for 12 consecutive months. Fatigue severity was measured using the fatigue severity subscale of the 20-item

Checklist Individual Strength (CIS20), which also contains subscales of physical activity, motivation, and concentration (24). The CIS fatigue consists of 8 items on fatigue symptom severity regarding the last 2 weeks and all items are scored on a 7-point Likert scale (range 8–56). Higher scores on the CIS fatigue indicate a higher level of fatigue experienced; a score of < 27 is considered normal and a score of ≥ 35 indicates severe fatigue (24). The CIS20 has proven to be a reliable and valid instrument in numerous conditions and was also used in RA (24,25).



Pain was assessed with the bodily pain subscale of the Short Form 36 health survey (SF-36), which asks about pain experienced in the last 2 weeks (26). The SF-36 bodily pain subscale consists of 2 items, one regarding pain level and one asking about the impact of pain on daily life. Final scores range from 0–100, with higher scores indicating less pain. For the purpose of the analyses, the SF-36 bodily pain scoring was inverted so that higher scores indicate more pain, whereas higher CIS scores indicated more fatigue. The SF-36 was adapted to cover a retrospective timeframe of 2 weeks, in order to make the interval similar to the interval of the CIS fatigue. At baseline and 12 months, pain was also assessed using a numerical rating scale.

During 2 weeks in the first month, the patients completed daily self-assessments of pain and fatigue using a self-observation list, with Likert scales asking about today (27). The Beck Depression Inventory for primary care (BDIPC) was used to classify patients for depression. The BDI-PC is a 7-item self-report instrument (range 0–21); a total score of ≥ 4 is suggestive of depression (28).

**Statistical analyses**

To assess whether fatigue changed over time on the group level, the course of fatigue over 1 year was analyzed graphically and using a longitudinal regression model (mixed model) correcting for repeated measures within patients, with CIS fatigue as the dependent variable and time as the independent variable. Next, 1-month changes in individual fatigue and individual pain scores were calculated over consecutive months. A scatter plot was made showing the individual monthly changes in pain and fatigue. Next, Pearson's correlations were used to analyze the correlations between monthly changes in pain and monthly changes in fatigue, at the same month and with a 1-month time lag. Finally, 3 longitudinal regression models (mixed models) were used to analyze the relationships between change in pain level and change in fatigue level over time, corrected for repeated measurements within the same patient. It was analyzed whether a change in pain was associated with a change in fatigue over the same month (Figure 1, model 1), or with a change in fatigue 1 month later (Figure 1, model 2), or with a change in fatigue 1 month earlier (Figure 1, model 3).

Age, sex, disease duration, rheumatoid factor positivity, HAQ score, and BDI-

PC score were considered as possible confounders. The monthly pain and fatigue absolute scores at the beginning of the monthly differences in fatigue were entered into the mixed model as covariates.

We also tested whether the associations differed by sex and age (effect modification). The assumptions of the linear mixed-model analysis were checked by testing the linear relationship between the difference in CIS fatigue and the predicted values and graphically using a scatter plot of the predicted values versus the residuals. Fatigue was the dependent variable in all 3 models to facilitate comparison of regression coefficients between the 3 models (Figure 1).

These analyses were repeated using the 2-week data set with daily changes in pain and fatigue. Data analysis was performed using the SAS system, version 9.20.

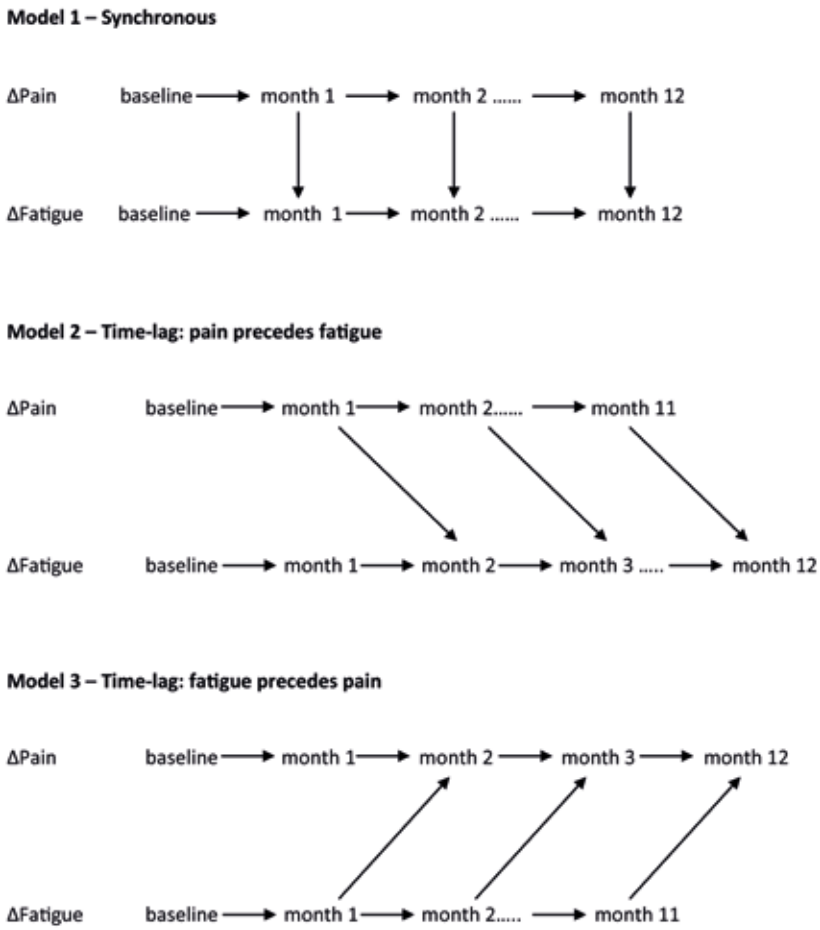


**Figure 1.** Schematic representation of the models used to analyze the longitudinal association between fatigue and pain.

## Results

### Patient characteristics

Two patients were excluded after the first measurement because of newly acquired sleep apnea and a malignant lung tumor. A total of 228 patients were included and 198 patients who filled in at least 10 monthly CIS fatigue and pain questionnaires were included in the analyses. The 30 patients who were not included in the analysis were not different in baseline characteristics from the 198 patients included in the analysis (data not shown). The included patients were mostly middle aged and the majority were women and rheumatoid factor positive (Table 1). Most patients had established disease, low levels of disease activity (DAS28 < 3.2), and low levels of disability (HAQ score). Clinical depression (BDI-PC score ≥ 4) seldom occurred.

At baseline, the mean pain score or pain severity was moderate and the mean level of fatigue was higher than normal (CIS fatigue score < 27), but lower than severe (CIS fatigue score ≥ 35) (24). Severe fatigue at baseline (CIS fatigue score ≥ 35) was experienced in 40% of the patients. There were no large differences between baseline and follow up in any of the variables.

### Medication

At baseline, 82 (41.4%) of 198 patients received disease-modifying antirheumatic drug (DMARD) monotherapy, most often with methotrexate (n=50), sulfasalazine (n=17), and azathioprine (n=5). Twenty-three (12%) of 198 patients received DMARD combination therapy, usually with methotrexate.

At baseline, 70 patients (35.4%) received a biologic agent and all were receiving tumor necrosis factor inhibiting agents, either as monotherapy or in combination with a DMARD. Eight patients (4%) stopped a biologic agent during the study and 12 (6%) started a biologic agent during the study. Thereby, 25 (13%) of 198 patients received oral prednisone. Medication use was missing in 23 patients.

### Fatigue and pain over time

The monthly CIS fatigue scores are shown for those patients who were severely fatigued at baseline, and for those with heightened and normal fatigue levels (24) (Figure 2A). The mean CIS fatigue score for the total group dropped a little within the 1-year period (Table 1); in the 3 subgroups, the mean fatigue scores remained stable over time. According to the linear mixed-model analyses, on average there was no change in the level of fatigue over time (P = 0.80) or in the level of pain over time (P = 0.10) (Figures 2A and B). Figure 2B shows the course of both the monthly CIS fatigue and pain scores of the total sample over 1 year.

**Table 1.** Patient characteristics at baseline and 12 months (n=198) *

| | baseline | 12 months |
|---|---|---|
| **Age, mean ± SD, years** | 56.7 ± 10.6 | |
| **Sex, no. ( % ) women** | 126 (64) | |
| **Disease duration, years** | 10 (6, 17) | |
| **Rheumatoid factor positivity, no. (%)** | 153 (77) | |
| **DAS 28, mean ± SD** | 3.16 ± 1.24 | 3.09 ± 1.21 |
| **VAS general health** | 30 (15, 46) | 25 (15,50) |
| **SJC28** | 3 (1, 6) | 4 (1, 6) |
| **TJC28** | 2 (0, 4) | 1 (0, 4) |
| **ESR, mm/hour** | 8 (4-18) | 10 (4-18) |
| **CRP level, mg/liter†** | 0 (0, 8) | 0 (0, 8) |
| **Pain: NRS pain severity (range 0-10), mean ± SD** | 4.29 ± 2.46 | 3.86 ± 2.55 |
| **Pain: SF-36 bodily pain (range 0-100),mean ± SD‡** | 35.23 ± 19.82 | 34.52 ± 21.34 |
| **CIS fatigue (range 8-56), mean ± SD** | 31.0 ± 12.4 | 30.0 ± 12.5 |
| **CIS fatigue, no. (%)** | | |
| **Normal fatigue (<27)** | 78 (39.4) | 87 (43.9) |
| **Heightened fatigue (27-34)** | 41 (20.7) | 35 (17.7) |
| **Severe fatigue (≥ 35)** | 79 (39.9) | 71 (35.9) |
| **HAQ DI score** | 0.63 (0.13, 1.13) | 0.63 (0.20, 1.13) |
| **Hemoglobin level, mean ± SD mmoles/ liter** | 8.21 ± 0.72 | 8.15 ± 0.78 |
| **BDI-PC score ≥ 4, no. (%)** | 10 (5) | 13 (6.6) |

* Values are the median (25th, 75th percentiles) unless otherwise indicated. DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; SJC28 = 28 swollen joint count; TJC28 = 28 tender joint count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NRS = numerical rating scale; SF-36 = 36-item Short Form health survey; CIS = Checklist Individual Strength; HAQ = Health Assessment Questionnaire; DI = disability index; BDI-PC = Beck Depression Inventory for primary care.† CRP levels <5 mg/liter are scored as 0. ‡ Scored on an inverted scale (where a higher score indicates less pain).

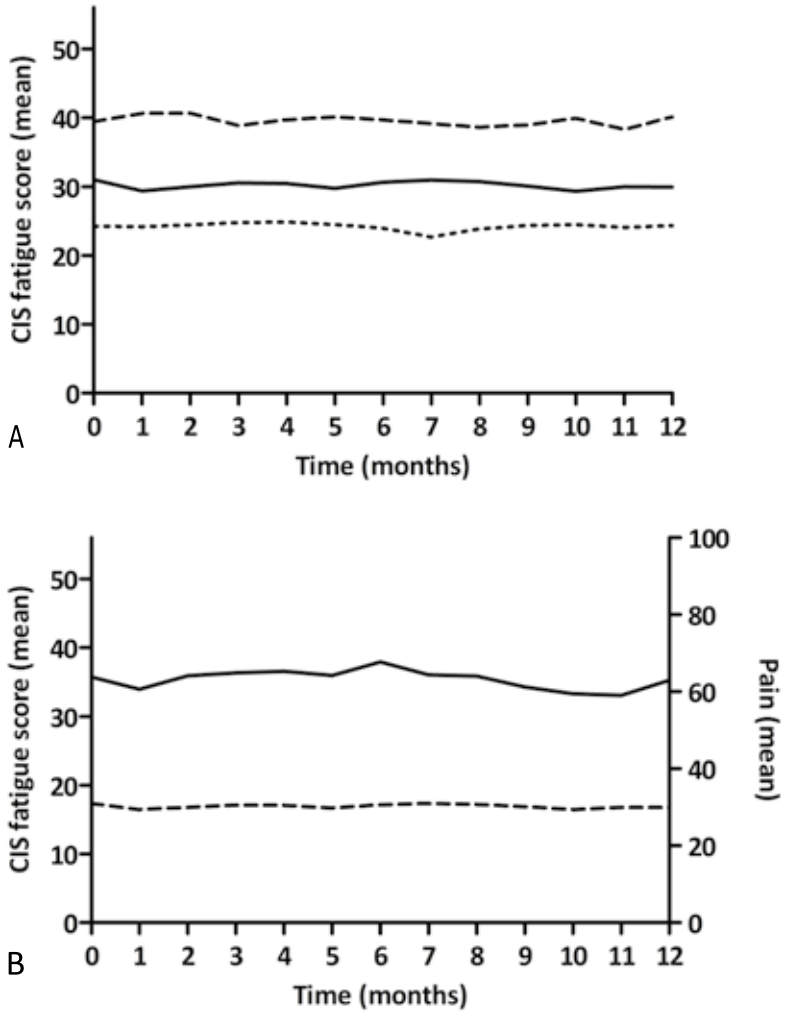


**Figure 2. A** Course of fatigue in patients with no, mild, and severe fatigue. Mean Checklist Individual Strength (CIS) fatigue scores over 12 months of the total group (n = 198; —), patients who were severely fatigued at baseline (n = 96; – – ), and patients who were not severely fatigued at baseline (n = 102;- -) are shown. **B**. The course of fatigue and pain over 1 year.

### Monthly changes in pain and fatigue: simple correlations

The "naive" association between all individual changes in pain and changes in fatigue, without correction for repeated measurements, is shown as a scatter plot in Figure 3. Each dot indicates a single time point with a monthly change in pain and a monthly change in fatigue, and each patient contributes up to 12 dots. From the graph it appears that there are fluctuations in pain and fatigue and that a change in fatigue is positively associated with a change in pain. On average,

there was no change in pain or fatigue; the mean ± SD monthly difference in pain was-0.02 ± 16.81 (P = 0.95) and the mean ± SD monthly difference in fatigue was -0.14 ± 8.12 (P = 0.41).

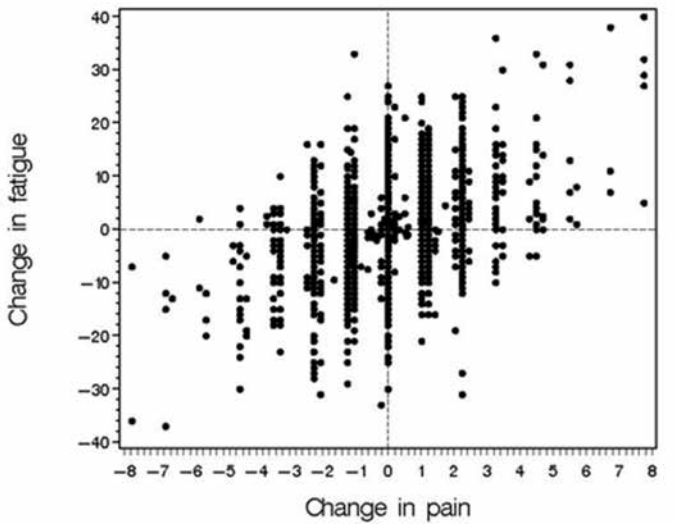


**Figure 3.** Scatterplot indicating the individual monthly changes in pain and changes in fatigue.

It can be seen in Table 2 that changes in pain and changes in fatigue in the same month have a positive correlation (r = 0.42), i.e., an increase or decrease in fatigue goes along with a change (increase or decrease) in pain in the same direction. It can also be seen that a change in pain in 1 month is negatively associated with a change in pain the next month (r =-0.41), i.e., an increase in pain is associated with a decrease in pain the next month. The same is found for fatigue (r = -0.39). The same kind of correlations are found for changes in fatigue preceding changes in pain (r =-0.21) and changes in pain preceding changes in fatigue (r = -0.15).

**Table 2.** Association between fatigue and pain with Pearson's correlation coefficients*

| | **Δ pain, same month** | | **Δ fatigue, 1 month earlier** | | **Δ pain, 1 month earlier** | |
|---|---|---|---|---|---|---|
| | **r** | **95% CI** | **r** | **95% CI** | **r** | **95% CI** |
| **Δ fatigue, same month** | 0.42 | 0.38, 0.45 | -0.39 | -0.43,-0.35 | -0.15 | -0.19,-0.11 |
| **Δ pain, same month** | --- | --- | -0.21 | -0.25,-0.17 | -0.41 | -0.44,-0.37 |

*Naïve correlations between monthly changes in fatigue and pain scores over 12 months. P<0.0001 for all. 95% CI= 95% confidence interval

**Monthly changes in pain and fatigue: longitudinal regression.**

For all regression models, adjustments were made for age, sex, and HAQ score, while monthly pain and fatigue scores were added as covariates. There were no large differences between the crude and the adjusted models, and only the results of the adjusted models are shown (Table 3).

The results of the first model, representing the association between change in pain and change in fatigue during the same month, showed a significant relationship ($P < 0.0001$). The positive beta coefficient ($\beta = 2.00$) indicated that more pain was associated with more fatigue during the same month.

The second model, analyzing the longitudinal association between change in pain level in the preceding month and change in fatigue 1 month later, indicated that a change in fatigue level was not related ($\beta = 0.12$, $P = 0.32$) to a change in pain level 1 month earlier. This indicates that an increase in pain level was not associated with an increase in fatigue level 1 month later.

Model 3, analyzing the longitudinal association between change in fatigue level in the preceding month and change in pain level 1 month later, also indicated that a change in fatigue level is not related ($\beta = -0.02$, $P = 0.83$) to a change in pain level 1 month later. This indicates that an increase in fatigue level is not associated with an increase in pain level 1 month later. When similarly analyzing the longitudinal association between change in daily pain and fatigue scores, the same results were found (data not shown). The associations between change in pain score and change in fatigue score were not significantly different for men and women, nor did they vary with age.

**Table 3.** Association between fatigue and pain over time with linear mixed-models analysis*

| | **β (95%CI)** | **P-value** |
|---|---|---|
| **Model 1: Δ fatigue = Δ pain in same month** | 2.00 (1.77, 2.21) | <0.0001 |
| **Model 2: Δ fatigue = Δ pain 1 month earlier** | 0.12 (-0.12, 0.36) | 0.32 |
| **Model 3: Δ fatigue = Δ pain 1 month later** | -0.02 (-0.25, 0.20) | 0.83 |

*A linear mixed-model analysis was performed, adjusted for age and sex, Health Assessment Questionnaire score, and the monthly pain and fatigue absolute scores at the beginning of the monthly differences in fatigue. 95% CI = 95% confidence interval.

## Discussion

This longitudinal study is the first study to examine the course of fatigue and pain in patients with RA in a period of 1 year with monthly measurements of fatigue and pain. The aim was to investigate whether changes in pain precede changes in fatigue, or vice versa, or whether pain and fatigue fluctuate together in time.

According to the results of this study, pain and fatigue showed monthly fluctuations that were synchronous rather than showing a temporal relationship with a time lag. Within the timeframe of 1 year and monthly assessments, as well as daily assessments in 2 weeks, the results do not indicate that one precedes the other. There also was no indication that the results would differ for age and sex. The results showed that pain and fatigue scores were quite stable over 1 year. However, within the patients there was considerable monthly fluctuation in pain scores and in fatigue scores that was synchronous rather than showing a temporal relationship with a time lag of 1 month. This was shown by the naive correlations of change that, however, were not controlled for confounders and the absolute scores at the baseline of each change. One of the consequences of this correction using the linear mixed models is that the time-lagged effects of the naive correlations "disappeared." Using the linear mixed-model analysis adjusted for age and sex, HAQ score, and monthly pain and fatigue scores at the beginning of the monthly differences in fatigue, the strongest association was found in the correlations and the regression model, reflecting synchronous changes in pain and fatigue. According to the regression coefficient, a 1-point increase in pain score (range 0–100) was associated with a 2-point increase in fatigue score (range 8–56). Until now, the minimally important difference for the CIS fatigue score is not formally known, but a comparison with the health transition question of the SF-36 using our own data suggested that a minimally important difference may be -5 for improvement and +3 for worsening (data not shown). In a trial of cognitive–behavioral therapy for RA, the mean decrease in CIS fatigue score was 5 in the intervention group and 2 in the control group (29). Therefore, the size of the relationship between pain and fatigue appears to be relevant.

The models using a time lag showed no significant association between chanes in pain and changes in fatigue. With this timeframe of 1 month, it cannot be said that one precedes or "causes" the other. To inform about probable causality, it would be informative if a change in pain precedes a change in fatigue (cause precedes effect) or vice versa. The time scale of such a temporal relationship between pain and fatigue is unclear and might be day to day or month to month (17–19). Since we were primarily interested in the course of fatigue over 1 year, we chose to assess fatigue and pain every month. The question, however, is whether monthly changes probably are too long. In a period of 2 weeks shortly

after baseline, patients filled in a diary with daily pain and fatigue scores. Therefore, we were also able to analyze a temporal relationship between pain and fatigue on a day-to-day basis. In the end, the results of the monthly analyses and the daily analyses were the same, i.e., a strong association of pain and fatigue at the same time point, with no recognizable time lag. We identified several studies that looked into the relationship between pain and fatigue using daily measurements in RA and in fibromyalgia (FM) (17,30 –32). It was found that patients with RA showed much variability in pain and fatigue levels within days, whereas there were no differences in pain and fatigue levels between days (17). It was suggested that the pattern of pain and fatigue was not explained by mood cycles (17). However, in another study of RA patients and consecutive daily fatigue assessments, it was found that days with more frequent positive events were related to lower levels of same-day fatigue and higher levels of next-day fatigue in women, but not for men (18). In a study of patients with RA, it appeared that diurnal fluctuations in fatigue were independent of the circadian rhythm of cortisol or inflammatory activity, but rather reflect temporal changes as a consequence of sleep, rest, and physical activity throughout the day (17,30). In FM, it appeared that there was a diurnal relationship between pain and fatigue that probably was mediated by stress or sleep quality (31,32). It may be worthwhile to evaluate sex differences; for example, it has been found that especially younger women with multiple daily roles seemed to be vulnerable to the negative impact of RA fatigue (33). However, in our study, no difference between men and women was found. To our knowledge, no previous studies have analyzed the longitudinal relationship between fatigue and pain in RA patients. The advantage of longitudinal analysis is that the individual development of both fatigue and pain in time can be investigated. There is one previous study, not in RA, in which the temporal relationship between pain and fatigue among primary care patients presenting with main symptoms of fatigue was analyzed (34). In this observational cohort study, pain and fatigue were measured at 1, 4, 8, and 12 months after baseline. The longitudinal associations were analyzed with 3 different models that were similar to those models used in the current study. The results indicated that changes in pain and fatigue are directly related in time, rather than showing a time lag in their relationship. This means that the findings of Nijrolder et al in the general care population are similar to the results of the current study (34).

A strength of our study is the monthly measurement of pain and fatigue during 1 year. By measuring pain and fatigue with relatively short time intervals, we consider that we had a reasonable precise measurement of the courses of pain and fatigue to analyze their longitudinal association. The recall period of fatigue and pain was 2 weeks because a recall period of 4 weeks is considered relatively long for patients to remember their fatigue and pain levels. The bodily pain sub-

scale of the SF-36 was modified to assess pain experienced in the last 2 weeks instead of the last 4 weeks to compare it with the CIS20, in which fatigue severity was assessed for the last 2 weeks. Another strength is few loss of data; 198 of the 228 patients filled in at least 10 monthly CIS fatigue and pain questionnaires. It was hypothesized that patients with a well-controlled comorbidity, such as regulated diabetes mellitus or regulated thyroid disease, would not experience extra fatigue from this underlying condition. Patients with multiple rheumatic diseases were not included; secondary Sjögren's syndrome was allowed and regarded as an extra-articular manifestation of RA.

A limitation of this study concerns the observational nature leading to a risk of confounding. However, in the adjusted model, we corrected for the most important confounders. No other confounders were identified. The patients were consecutively included at regular visits, not at indication of having high pain levels or high fatigue severity. Therefore, large changes in fatigue and pain after baseline were not found; on the other hand, the sample is representative for the RA population regarding levels of pain and fatigue. Another important consideration is the different scaling for measuring pain and fatigue. The SF-36 bodily pain subscale was used to assess pain instead of a single pain visual analog scale because the subscale is composed of 2 items, which may be more valid than 1 item. However, these 2 items have a limited number of response options, which may make it difficult to detect smaller changes in pain. One of the pain items considers the impact of pain on daily life, but it may not confound a relationship of pain with fatigue because the CIS fatigue subscale is about symptom severity, and impact on daily life is assessed using other CIS subscales.

Seeing the important meaning of pain and fatigue for patients with RA, reductions of pain and fatigue are recommendable goals for RA management (10). Further research is recommended in factors that can cause or perpetuate fatigue in RA. Although pain could probably "cause" fatigue or fatigue could probably "cause" pain, probably both pain and fatigue are driven by common factors. Common factors maybe psychological factors, which could be investigated by a multidimensional model of fatigue using structural equation modeling.

In summary, the results of this 12-month longitudinal study of the monthly temporal relationship between pain and fatigue show that in established RA, pain and fatigue have a synchronous association with a fluctuating pattern around an individual mean, rather than showing temporal associations. There is no indication that one precedes or causes the other, regardless of the time scale being days or months. The clinical implication is that both manifestations should be treated because it cannot be expected that an improvement in one is followed by an improvement in the other.

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# Chapter 3

# Relationship between objectively assessed physical activity and fatigue in patients with rheumatoid arthritis: inverse correlation of activity and fatigue

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## Abstract

### Objective

Fatigue is generally associated with low physical activity in patients with various chronic medical conditions. However, such an association has not been reported among patients with rheumatoid arthritis (RA). The objectives of this study were to investigate whether daily activity level is associated with fatigue in patients with RA, and whether pain, disability, coping, and/or cognition are associated with the level of daily activity.

### Methods

Patients with RA who visited our outpatient clinic were recruited consecutively. Fatigue severity was measured using the Checklist Individual Strength (CIS20). Physical activity was measured for 14 consecutive days using an ankle-worn actometer. The daily activity level of each patient was calculated, and each patient was classified as having a low or high activity level with respect to the group average. Data were analyzed by linear regression.

### Results

A total of 167 patients were included in the analysis; 25% had a low activity level and 75% had a high activity level. A regression analysis revealed that higher activity levels were associated with reduced fatigue ($P = 0.008$). The mean ± SD CIS fatigue score was 30.9 ± 12.3 among the patients with a high activity level and 35.7 ± 12.8 among the patients with a low activity level ($P = 0.03$). Pain, disability, coping, and cognition were not associated significantly with daily activity level.

### Conclusion

Among patients with RA, a higher level of daily physical activity was associated with reduced levels of fatigue. This relationship was not explained by differences in sex, age, disease duration, pain, disability, or other fatigue-related factors.

## Introduction

Fatigue is a common symptom among patients with rheumatic diseases, including rheumatoid arthritis (RA) (1). As many as 40% of patients with RA experience severe fatigue (defined as a Checklist Individual Strength (CIS) fatigue score ≥35), and fatigue often causes debilitating and restricted daily functioning (2–6).

In patients with RA, fatigue can be associated with pain, disability, depressive thoughts, anxiety, worrying, feelings of helplessness, reduced self-efficacy, sleep disturbances, and limitations in social functioning (7–9). Based on these findings, pain and disability, and not inflammation per se, and psychosocial factors may be important contributors to the presence and persistence of fatigue. In addition, it remains unclear which treatments are effective for treating fatigue in RA patients. This uncertainty can contribute to fatigue being neglected during health care visits. However, some randomized controlled trials (RCTs) suggest that both cognitive–behavioral therapy and physical exercise can be effective for treating fatigue in patients with RA (10,11).

With respect to chronic fatigue syndrome (CFS), graded exercise training and cognitive–behavioral therapy are the only 2 interventions that are considered to be effective (12–15). Patients with CFS are significantly less physically active compared to age-matched healthy controls (16–18), and CFS patients with "persistently passive" daily activity patterns are more inclined to avoid physical exertion and experience more physical dysfunction (18). In this respect, "persistently passive" patients were defined as patients with an activity level that was lower than the group average for at least 90% of the total observation period; the remaining patients were defined as "active" (18).

Decreased levels of physical activity have been reported among patients with RA (19–26). For example, an international study reported that the majority of patients with RA did not engage in regular physical exercise (with physical exercise defined as ≥30 minutes of exercise with some shortness of breath and/or perspiration) (23). The percentage of Dutch patients with RA who met the recommendation for physical activity was similar to the general population; however, among participants ages 45–64 years, the average number of minutes per week performing physical activity was significantly lower in the RA patient population than in the general population (19). Both the belief that physical activity can help manage the disease and increased motivation to engage in physical activity can drive higher levels of physical activity among the RA population (27). Among other patient groups, including patients with multiple sclerosis, increased physical activity (measured objectively) has been associated with decreased fatigue (28).

With respect to RA, daily physical activity has not been measured objectively, and it is unclear whether fatigue and physical activity are correlated. Daily phys-

ical activity can also be influenced by pain, disability, coping, and/or cognition. Clarifying how these factors can influence activity levels may provide important clues for developing an effective treatment for fatigue in patients with RA. Daily physical activity can be measured objectively using actigraphy, providing a reliable, valid measure of human physical activity (17,29).

The objectives of this study were to investigate whether objectively measured activity levels and activity patterns are associated with fatigue levels in patients with RA, and whether pain, disability, coping, and/or cognition are associated with, or influence, the level of activity among patients with RA.

## Materials and methods

### Design

This cross-sectional study was part of a cohort study that was designed to determine which factors are associated with fatigue in RA. The study was approved by the Medical Ethics Committee Arnhem-Nijmegen in The Netherlands, and all participants provided written informed consent.



### Included patients

From June 2006 through October 2007, consecutive patients ages 18–75 years who visited their rheumatologist at the outpatient clinic of the Radboud University Medical Center at Nijmegen were invited to participate. Patients were informed by either their rheumatologist or nurse specialist, and the information was provided both verbally and in writing.

Inclusion criteria included a diagnosis of RA in accordance with the 1987 ACR classification criteria (30), age 18–75 years, and the ability to read and write Dutch. Patients were excluded from the study if they had a second rheumatic disease, a history of malignancies and/or other chronic fatigue–related comorbidity, or a current diagnosis of depression, or were currently receiving psychological or psychiatric treatment. Patients with a comorbidity that was well controlled were eligible to participate; such comorbidities included regulated thyroid disease (free T4 ≥ 8 pmoles/liter and thyroidstimulating hormone ≤ 1.0 unit/liter), controlled diabetes mellitus (with normalized urine and blood glucose values of 45–66.6 mg/dl and 72–100.8 mg/dl, respectively, and glycosylated hemoglobin values < 8.0%), mild nonrestrictive chronic obstructive pulmonary disease, and successfully treated nonmetastasized basal cell carcinoma or squamous cell carcinoma in the skin.

### Data collection

Patient characteristics (sex, age, and body mass index (BMI)), disease characteristics (disease duration and rheumatoid factor), comorbidity, and medication use were recorded by research nurses at the time of inclusion in the study. Blood samples were obtained and used to determine erythrocyte sedimentation rate, C-reactive protein level, and hemoglobin level. Upon inclusion, disease activity was assessed by the rheumatologist or by a specialized rheumatology nurse using the Disease Activity Score in 28 joints. At inclusion, psychosocial variables, including beliefs regarding the somatic and nonsomatic causes of fatigue, coping strategies, and catastrophizing, were recorded using patient questionnaires that were answered using a computer. Daily activity was recorded objectively using an actometer for 14 consecutive days immediately following inclusion.

Fatigue among patients with RA could have multiple determinants, and previous studies using multidimensional models have documented the importance of variables such as mood, coping processes, and self-efficacy (4,31). Therefore, we collected a set of psychosocial variables that could potentially influence fatigue.

Fatigue severity was assessed using the fatigue severity subscale of the CIS20 (31). The CIS fatigue subscale consists of 8 items, each of which is scored using a 7-point Likert scale (yielding a total score of 8–56). The 8 items are designed to measure the patient's fatigue level during the previous 2 weeks, with a higher score on the CIS fatigue indicating a higher level of fatigue. A total score of ≥ 35 (which is 2 SDs above the mean score for a healthy control group) indicates severe fatigue (31). The CIS20 has been validated and is considered reliable under many conditions; this checklist also has been used previously to assess patients with RA (8,31).

Pain was assessed using the bodily pain subscale of the Short Form 36 (SF-36) health survey, which determines the patient's pain severity and pain-related limitations experienced during the previous 4 weeks (32). The SF-36 bodily pain subscale score ranges from 0–100, with a higher score indicating less severe pain and fewer pain related limitations. Pain severity was also assessed using a numerical rating scale regarding pain in the current situation (range 0–10, where 0 = no pain and 10 = extreme pain).

Daily functioning was assessed using the Health Assessment Questionnaire (HAQ) disability index and the physical functioning subscale of the SF-36 (33).

The Beck Depression Inventory for primary care (BDIPC) was used to classify patients for clinical depression(34). The BDI-PC is a 7-item self-reporting instrument that is scored by totaling the highest scores from each of the 7 individual items. Each item is rated on a 4-point scale (ranging from 0–3); therefore, the maximum total score for the BDI-PC is 21. A total score of ≥ 4 on the BDI-PC indicates clinical depression (34).

Beliefs regarding the somatic and nonsomatic causes of fatigue were measured using a modified version of the Causal Attribution List. Self-efficacy with respect to fatigue was measured using the Self-Efficacy Scale 28, a questionnaire containing 7 items that are scored on a 4-point Likert scale.

Coping strategies were measured using the Modified Pain Coping Inventory for Fatigue (MPCI-F), which is scored on a 4-point Likert scale and is based on the Pain Coping Inventory. In the MPCI-F, "pain" is replaced with "fatigue".

To assess catastrophizing, the Fatigue Catastrophizing Scale (FCS) was used. The FCS was derived from the Pain Catastrophizing Scale, with the word "pain" replaced with "fatigue" (35).

Daily physical activity, including general daily activities at home, at work, during rest, and during leisure time, was measured using an actometer (Actilog

version 4.1), an ankle-worn motion-sensing device that registers and quantifies daily physical activity (17,18). The actometer contains a piezoelectric sensor that is sensitive in 3 directions. Acceleration of the sensor above a predefined threshold (the actometers were all calibrated to have the same threshold) is considered to be activity and is stored in the device's internal memory. The actometer's counter was read and reset each second by the microcontroller, which added the value to an integration counter that was set to 5 minutes. Therefore, the activity score was measured every 5 minutes, with a maximum of 300 scores counted.

Each actometer was calibrated before collecting data. The actometer's output was an activity count that was the weighted sum of the number of accelerations measured during a 5-minute period. To obtain a valid measurement of the patient's daily activity, the patient was instructed to wear the actometer for 14 consecutive days and to remove it only during swimming and bathing; therefore, all activities throughout the day (except swimming and bathing) were recorded.



**Actometer data**

If a non–actometer-wearing period exceeded 3 hours, the day was recorded as "nonvalid." Patients with >2 nonvalid registration days were excluded from the analysis; in case of 1 or 2 nonvalid days, data for these days were inserted using the mean values of the remaining 10 or 11 valid days. Individual physical activity was analyzed using the Actilog Analyzer software, version 4.10. The mean physical activity score of all included patients was calculated to determine the average daily physical activity over the entire 12-day period, and this was expressed as the average number of accelerations per 5-minute interval. To subtype activity levels among the patients with RA, we assigned each patient to 1 of 2 groups: patients with low daily physical activity and patients with high daily physical activity.

In accordance with van der Werf et al, the patients with a low activity level were defined objectively as those patients whose activity level was lower than the group average for at least 90% of the total observation period; the remaining patients were defined as having a high daily activity level (18). Figure 1 shows examples of the daily activity pattern of a patient with a high daily activity level (Fig.1A) and a patient with a low daily activity level (Fig.1B).

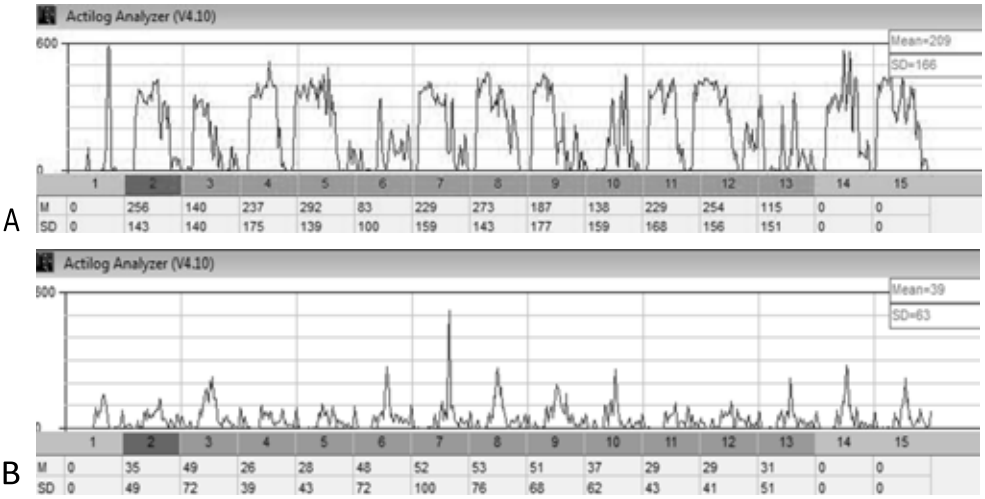


**Figure 1. A**, A rheumatoid arthritis (RA) patient with a high activity level. **B**, A RA patient with a low activity level. The y-axis shows the activity count and the x-axis shows the day number and the mean physical activity during each day (M). The mean activity levels of all valid days and their SDs are shown in the top right-hand corner of each graph. The dark gray box is the first valid registration day (day 2).

### Statistical analysis

Baseline differences between the high and low daily activity level groups were analyzed using Student's t-test, the Mann-Whitney U test, or the chi-square test, where appropriate. To determine whether there was an association between fatigue and daily physical activity, continuous and dichotomous (low and high activity level) linear regression analyses were performed, with CIS fatigue score as the dependent variable and daily physical activity as the independent variable, with correction for potential confounders. Age and sex were predetermined for inclusion in the adjusted linear regression model, whereas all other variables were considered to be confounders if the regression coefficient of the main effect (daily physical activity) in the linear regression model changed by ≥ 10% after adding the variable (one of the baseline characteristics) (Table 1) to the model.

To analyze the association between fatigue and activity score divided into equal group sizes, we performed a sensitivity analysis using a linear regression analysis with activity divided into quartiles. The association between activity level (low and high) and the occurrence of fatigue (severe and not severe) was also analyzed in a 2 x 2 table using the chi-square test; for this analysis, fatigue was classified as either severely fatigued (CIS fatigue score ≥ 35) or not severely fatigued (CIS fatigue score < 35) (6). All analyses were performed using the PASW statistics package, version 18.0 (SPSS).

## Results

### Patients

Of the 230 patients who were included in the study, 181 (78%) were willing to wear an actometer for 14 consecutive days. The first and last days of data collection were excluded from the analysis, yielding 12 complete continuous days of data. One hundred sixty-seven (92%) of these 181 patients had at least 10 daily measurements of activity and were included in the analysis (Table 1). We found no statistically significant difference in baseline characteristics between the 49 patients who were unwilling to wear an actometer and the 181 patients who agreed to wear an actometer, nor did we find a difference between the 14 patients with an insufficient number of daily measurements and the 167 patients who were analyzed (data not shown). Based on our definition (see Methods), 42 patients were classified as having a low activity level, and the remaining 125 patients were classified as having a high activity level.



**Table 1.** Baseline characteristics of 167 patients with RA with a low or high daily activity level*

| | Low activity level (n=42) | High activity level (n=125) | P-value |
|---|---|---|---|
| **Age, years** | 56.78 (11.03) | 54.79 (10.59) | 0.30 |
| **Female sex, no. (%)** | 33 (79) | 67 (54) | 0.004† |
| **Body mass index, median (IQR) kg/m2** | 26.72 (24.34-29.04) | 24.51 (22.69-26.68) | 0.004† |
| **Positive rheumatoid factor, no. (%)** | 31 (73.8) | 92 (73.6) | 0.99 |
| **Disease duration, median (IQR) years** | 9.5 (6-17.25) | 10 (5.0-16) | 0.43 |
| **Cardiovascular disease, no. (%)** | 6 (14) | 18 (14) | 0.99 |
| **COPD, no. (%)** | 0 (0) | 5 (4) | 0.19 |
| **Diabetes mellitus, no. (%)** | 1 (2.4) | 8 (6.4) | 0.32 |
| **DMARD use, no. (%)** | 33 (78.6) | 110 (88) | 0.13 |
| **Biologic agent use, no. (%)** | 18 (42.9) | 43 (34.4) | 0.33 |
| **Corticosteroids, no. (%)** | 11 (26.2) | 31 (24.8) | 0.86 |
| **Statin use, no. (%)** | 3 (7.1) | 3 (2.4) | 0.15 |
| **DAS28 (range 0–10)** | 3.28 (1.18) | 3.07 (1.23) | 0.32 |
| **Swollen joint count 28 (range 0–28), median (IQR)** | 3 (2-6) | 3 (2-6) | 0.65 |
| **Tender joint count 28 (range 0–28), median (IQR)** | 2 (1-4.25) | 1 (0-4) | 0.24 |
| **ESR, median (IQR) mm/hour** | 8 (4-16.5) | 7 (4-13) | 0.31 |

| | Low activity level (n=42) | High activity level (n=125) | P-value |
|---|---|---|---|
| **CRP, median (IQR) mg/liter‡** | 0 (0-8.75) | 0 (0-6) | 0.26 |
| **Hemoglobin, mg/dl** | 147.6 (10.27) | 149.37 (16.76) | 0.89 |
| **NRS pain severity (range 0–10)** | 4.76 (2.69) | 4.26 (2.36) | 0.25 |
| **SF-36 bodily pain (range 0–100)** | 63.94 (18.62) | 63.61 (19.07) | 0.96 |
| **CIS fatigue (range 8–56)** | 35.74 (12.84) | 30.88 (12.27) | 0.03† |
| **HAQ DI (range 0–3)** | 0.80 (0.56) | 0.65 (0.60) | 0.16 |
| **SF-36 physical functioning (range 0–100)** | 56.31 (23.56) | 59.96 (24.20) | 0.40 |
| **SF-36 social functioning (range 0–100)** | 73.51 (21.60) | 75.60 (23.43) | 0.66 |
| **SCL-90 sleep disturbances (range 3–15)** | 6.31 (2.98) | 5.90 (2.92) | 0.24 |
| **Depression, BDI-PC 4, no. (%)** | 0 (0%) | 9 (7.2%) | 0.56 |
| **CAL somatic (range 3–12), median (IQR)** | 6 (5-7) | 6 (6-7.5) | 0.24 |
| **CAL nonsomatic (range 3–12)** | 9.1 (1.82) | 8.66 (1.95) | 0.21 |
| **SES28 (range 7–28)** | 18.83 (3.75) | 19.73 (3.55) | 0.17 |
| **MPCI-F worrying (range 9–36), median (IQR)** | 14 (11-17.3) | 14 (11-17) | 0.72 |
| **MPCI-F retreating (range 7–28)** | 12.62 (3.95) | 11.84 (3.67) | 0.24 |
| **MPCI-F resting (range 5–20)** | 12.24 (2.99) | 11.41 (2.93) | 0.12 |
| **MPCI-F fatigue transformation (range 4–16)** | 8.71 (2.45) | 8.32 (2.53) | 0.37 |
| **MPCI-F reducing demands (range 3–12)** | 6.14 (1.84) | 6.67 (2.01) | 0.13 |
| **MPCI-F distraction (range 5–20)** | 11.93 (2.40) | 11.06 (3.22) | 0.06 |
| **FCS rumination (range 0–16)** | 3.86 (3.75) | 4.46 (3.77) | 0.37 |
| **FCS helplessness (range 0–24)** | 3.60 (4.42) | 4.07 (4.27) | 0.35 |
| **FCS magnification (range 0–12)** | 0.88 (1.74) | 1.17 (1.91) | 0.28 |

*Values are the mean (SD) unless indicated otherwise. IQR = interquartile range; COPD = chronic obstructive pulmonary disease; DMARD = disease-modifying antirheumatic drug; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NRS = numerical rating scale; SF-36 = Short Form 36 health survey; CIS = Checklist Individual Strength; HAQ = Health Assessment Questionnaire; DI = disability index; SCL-90 = Symptom Checklist-90; BDI-PC = Beck Depression Inventory for primary care; CAL = Causal Attribution List; SES28 = Self-Efficacy Scale 28; MPCI-F = Modified Pain Coping Inventory for Fatigue; FCS = Fatigue Catastrophizingn Scale.† Statistically significant.‡ CRP levels 5 mg/liter were scored as 0.

## High daily activity level versus low daily activity level

### Univariate analyses

Of the 167 patients with RA who were included in the analysis, 44% were severely fatigued (CIS fatigue score ≥ 35), and the overall mean ± SD CIS fatigue score was 32.1 ± 12.6. The mean ± SD daily physical activity score of 167 patients was 73 ± 27. Therefore, the average activity level of patients with RA lies between

healthy controls and patients with CFS, and is similar to other chronic conditions (Table 2). The RA patients with a high activity level had a mean ± SD daily activity score of 83 ± 23, and the patients with a low activity level had a mean ± SD daily activity score of 43 ± 9. Table 1 summarizes separately the clinical characteristics of the 42 low activity (25%) and the 125 high activity (75%) patients with RA. Our analysis revealed no significant difference between the high activity and low activity groups with respect to comorbidity or medication use. Conversely, the high activity patients had significantly lower CIS fatigue scores than the low activity patients. Moreover, the low activity patient group had significantly higher BMI scores and a significantly higher percentage of women. No differences were detected between the 2 groups with respect to other characteristics, including pain, disability/function, and any of the variables that reflect coping and cognition.



**Table 2.** Overview of studies that measured daily physical activity using an ankle-worn accelerometer, with activity count as the outcome measure*

| Study | Participants (n) | Total no. of registered days | Activity count, mean ± SD |
|---|---|---|---|
| **current study** | RA patients (167) | 12 | 73 ± 27 |
| **van der Werf et al, 2000 (18)** | Chronic fatigue syndrome (277) | 12 | 66 ± 22 |
| | Healthy controls (47) | 12 | 91 ± 25 |
| **Servaes et al, 2002 (42)** | Severely fatigued disease-free patients with breast carcinoma (57) | 12 | 76.1 ± 22.5 |
| | Non-severely fatigued disease-free patients with breast carcinoma (93) | 12 | 79.1 ± 20.8 |
| | Patients without a history of breast carcinoma (78) | 12 | 76.9 ± 15.5 |
| **Steele et al, 2003 (41)** | COPD patients (41) | 5 | 87.4 ± 38.8 |

* RA = rheumatoid arthritis; COPD = chronic obstructive pulmonary disease.

## Relationship with fatigue

To analyze the relationship between activity level and fatigue, both age and sex were predetermined for inclusion in the adjusted linear regression model, in which BMI, pain severity, and the HAQ were included as confounders. The analysis revealed that the relationship between activity and fatigue was linear (Table 3), with each unit increase in activity correlating with a 0.08 decrease in the fatigue score. To facilitate the interpretation of these results, Figure 2 shows box plots of the fatigue levels of the low and high daily activity level groups. The plot

shows that the median CIS fatigue score of the low activity patients was higher than the median CIS fatigue score of the high activity patients (36 versus 31; P = 0.03).

Table 4 summarizes the results of the linear regression analysis between low and high activity, adjusted for age, sex, HAQ, BMI, and pain. The table shows that high activity patients with RA scored an average of 4 points lower for fatigue than low activity patients with RA. The CIS fatigue score is usually divided into severe fatigue (CIS ≥35) and elevated/normal fatigue (CIS <35). A chi-square test revealed a significantly higher percentage of severely fatigued (i.e., CIS ≥35) patients in the passive group than in the active group (60% versus 38%; P = 0.017).

## Sensitivity analysis

Table 4 also shows the linear regression analysis of sensitivity with activity divided into quartiles; this analysis was adjusted for age, sex, HAQ, BMI, and pain. Significantly higher fatigue scores (P < 0.001) were found between the low activity patients (i.e., the first quartile) and the high activity patients (i.e., the fourth quartile).

**Table 3.** Linear regression model of fatigue (continuous) versus daily activity (continuous)*

| | B | P-value | 95% CI |
|---|---|---|---|
| **Unadjusted model** | | | |
| **Constant** | 38.49 | <0.001 | 32.94, 44.04 |
| **Activity** | -0.087 | 0.017 | -0.158,-0.016 |
| **Adjusted model†** | | | |
| **Constant** | 49.90 | <0.001 | 34.62, 65.19 |
| **Activity** | -0.082 | 0.008 | -0.14,-0.021 |

* P values and 95% confidence intervals (95% CIs) are based on the regression coefficient. B = regression coefficient; constant = intercept. † The adjusted model was corrected for age, sex, the disability index of the Health Assessment Questionnaire, body mass index, and the numerical rating scale for pain.

**Table 4.** Results of the unadjusted and adjusted linear regression models of fatigue (continuous) for low versus high activity*

| | B | P-value | 95% CI |
|---|---|---|---|
| **Unadjusted model** | | | |
| **Constant** | 35.74 | <0.001 | 31.96, 39.52 |
| **High activity level** | -4.86 | 0.03 | -9.23,-0.49 |
| **Adjusted model†** | | | |
| **Constant** | 46.20 | <0.001 | 31.94, 60.47 |
| **High activity level** | -4.42 | 0.018 | -8.059,-0.78 |
| **Adjusted model (divided into quartiles)†** | | | |
| **Constant** | 41.331 | <0.001 | 28.47, 54.19 |
| **First quartile** | 5.698 | 0.014 | 1.16, 10.24 |
| **Second quartile** | 3.467 | 0.126 | -0.99, 7.92 |
| **Third quartile** | 0.198 | 0.928 | -4.10, 4.50 |
| **Fourth quartile** | 0 | NA | NA |

* P values and 95% confidence intervals (95% CIs) are based on the regression coefficient. B = regression coefficient; constant = intercept; NA = not applicable. † The adjusted model was corrected for age, sex, the disability index of the Health Assessment Questionnaire, body mass index, and the numerical rating scale for pain.

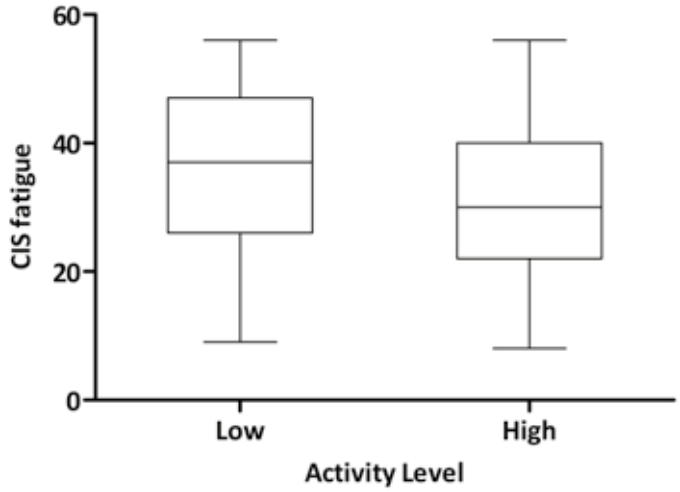


**Figure 2.** Box plots of the Checklist Individual Strength (CIS) fatigue scores are shown for the 2 activity groups. The bold horizontal bars indicate the median and the upper and lower boxes indicate the quartiles. The whiskers indicate the minimum and maximum values

## Discussion

Based on the results obtained from this study, patients with RA who have a high level of daily physical activity have less fatigue than patients with low daily physical activity; moreover, the level of activity is not associated with pain, disability, coping, or cognition.

Activity level was measured objectively, and patients who had an activity level that was lower than the group average for more than 90% of the observation time were defined as having a low activity level (see Methods). Therefore, the classification of each patient into either the low or high activity group was based on the activity of his/her fellow patients. The majority of patients (75%) were classified as having high activity and the remaining 25% were classified as having low activity. Overall, nearly half of all patients had severe fatigue, as determined using the CIS questionnaire. According to the CIS definition of severe fatigue, this means that many of the RA patients in this study had a fatigue level that was similar to the level in patients with CFS. Based on the regression analysis, higher activity scores were associated with lower fatigue scores, even after correcting for potential confounders.

Consistent with this analysis, the average fatigue score among patients with high activity was 5 points lower than that for patients with low activity. This difference is likely relevant, as a trial that examined the effect of cognitive behavioral therapy in RA patients reported a 6-point difference in CIS fatigue score between the 2 groups (36).

In addition to higher fatigue levels, RA patients who have more pain and disability would likely have lower average levels of activity. Moreover, activity level can also be associated with coping and cognition; patients with “passive” or “unproductive” coping styles can also have lower levels of activity. However, our results revealed no strong indication that either coping or cognition is correlated with activity level. Notably, coping, cognition, pain, and disability are all associated with fatigue in patients with RA (8).

To the best of our knowledge, this is the first study to objectively measure and relate the level of physical activity and fatigue in patients with RA. A few other studies have investigated the association between physical activity and fatigue, and none of these studies included patients with RA. It is important to note that decreased physical activity has been associated with increased fatigue in patients with CFS, Sjögren’s disease, and breast cancer (37,38).

Nevertheless, one cannot necessarily conclude that “passiveness” causes fatigue (or vice versa). Indeed, both scenarios are conceivable; fatigue may lead to decreased activity, and decreased activity may lead to fatigue. To address the possibility of a clinically relevant causal relationship, an RCT should be per-

formed. For example, one can test whether increasing activity through exercise and/or training can reduce fatigue in severely fatigued RA patients with low daily activity (12).

One question that remains is whether RA patients have low levels of fatigue relative to healthy subjects and/or the general population. Although several studies have investigated the activity levels of RA patients, comparing the findings across studies is problematic because of differences in the assessment methods (e.g., assessment by questionnaire versus objective measurements) (19–26,39). Based on the published literature, patients with RA appear to have a relatively low level of physical activity. In particular, a study comparing RA patients from various countries found that up to 80% of patients in some countries were "physically inactive" (23); the authors defined "physically active" as ≥ 30 minutes of exercise with at least some shortness of breath and/or perspiration (23).



The type of accelerometer that we used in this study has been used in other studies, including studies with healthy controls and other patient groups (Table 2). Therefore, the group averages can be compared (albeit indirectly), although groups may not be fully comparable with respect to age or sex. Nevertheless, the activity level of patients with RA lies somewhere between the activity level of patients with CFS and healthy controls, but lower than the activity level of patients with breast cancer or Sjögren's syndrome. Moreover, compared to healthy controls, patients with chronic diseases have decreased daily activity levels, including patients with diabetes mellitus (40), Sjögren's syndrome (37), chronic obstructive pulmonary disease (41), breast carcinoma (42), and hereditary motor and sensory neuropathy type 1 (43).

The strength of our study is the large number of patients and the measurement of daily activity for 12 consecutive days. In addition, because nonrandomized studies always carry a risk of confounding, the analyses were adjusted for several confounding factors. Because the difference between the adjusted and unadjusted models was negligible, it is unlikely that any residual confounding factors biased the association. Moreover, actigraphy (i.e., the use of a uniaxial actometer) is a reliable and valid instrument for continuously and objectively measuring physical activity (18,29,44). However, a limitation is that the actometer results cannot be reliably correlated to energy expenditure (45). Therefore, patients with a low daily activity level should be advised to increase their physical activity, although we cannot precisely define or recommend how many minutes one should be physically active; thus, current recommendations advise patients to engage in physical activity for ≥ 30 minutes/day, ≥5 days/week.

Another limitation of our study might be the substitution of missing actometer values with the mean values of the remaining 10 or 11 days. However, because only 7 (4.2%) of the 167 patients had 1 or 2 missing values, the effect of

this approach was likely negligible. Another limitation could be the cross-sectional design of this study. To determine whether the relationship between fatigue and daily activity level is causal, it would have been an advantage if longitudinal data could be used. If changes in daily activity level would precede changes in fatigue, this could be interpreted causally. A stronger design to determine causal relationships, however, is an RCT.

In summary, we report that the level of activity and the level of fatigue are associated in patients with RA; however, which factors influence the level of activity in RA patients remains unclear. With respect to fatigue in RA patients, which treatments are effective also remains unclear. Nevertheless, reducing pain and inflammation should have high priority in managing RA, and reducing pain may also reduce fatigue. However, RA patients whose disease is managed well can still develop severe fatigue (6). In addition to the association between fatigue and decreased activity revealed here, fatigue can also be associated with pain, disability, coping, and cognition (7–9). RCTs have suggested that cognitive behavioral therapy and physical exercise can be beneficial in treating fatigue in RA patients (10,11). Although several RCTs found that exercise is beneficial for RA patients (46), only one relatively small trial found that exercise may be beneficial specifically for fatigue in RA patients (10). Evidence from studies of CFS also suggests that exercise may be beneficial for RA patients (10,47). Exercise might be particularly relevant to patients with low daily activity levels. For relatively active patients, other factors, such as changing dysfunctional beliefs with respect to fatigue or reducing their “all-or-nothing” behavior, may be more important (48). Future studies should investigate whether fatigue in patients with RA can indeed be treated effectively with exercise or another form of graded activity, particularly among patients who have a low level of physical activity and chronic severe fatigue.

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# Chapter 4

# Comparison of physical activity and level of fatigue among patients with rheumatoid arthritis and the general Dutch population

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## Abstract

### Objective

Many rheumatoid arthritis (RA) patients experience severe fatigue and have low levels of physical activity. However, it is unclear how levels of fatigue and physical activity in RA compare to the general population. Objectives of this study: 1) compare the level of physical activity and the level of fatigue between RA patients and the general Dutch population, 2) investigate factors associated with self-reported physical activity in RA and 3) describe sport activities of RA patients and their limitations to participate in sports.

### Methods

A sample of the general Dutch population was obtained as part of the Nijmegen Biomedical Study (n=3764); fatigue and physical activity were self-assessed. Across the Netherlands, 740 RA patients filled out an online survey in 2013 and 2014 on physical activity. Fatigue was assessed in 228 RA patients from the Nijmegen RA cohort (2006-2007).

### Results

RA patients reported lower physical activity per week (median 24.6 hours) than the general population (median 33.0 hours) and RA patients had a significant higher fatigue level according to the Shortened Fatigue Questionnaire (16 versus 9, range 4-28). In RA, lower level of physical activity was associated with older age and longer disease duration. Fitness, swimming, strength training and walking were the most popular sports among RA patients. Most frequently mentioned limitations were physical impairment, not aware of the options, fear of injuries.

### Conclusion

Compared to the general Dutch population, RA patients showed higher levels of fatigue and were less physically active. RA patients should be encouraged to increase physical activity with as consequence a possible reduction in fatigue.

## Introduction

Fatigue is a frequent complaint in patients with Rheumatoid Arthritis (RA), even among patients with low and moderate levels of disease activity (2, 3). As much as 40% of the patients with RA may have severe fatigue (2). Moreover, fatigue in RA is a patient-relevant complaint: patients with RA express their fatigue as unpredictable, overwhelming and different from normal tiredness (3) and it is often perceived as debilitating and restricting daily functioning (2, 4-6). Fatigue in RA potentially has a large impact on quality of life and patients give high priority to fatigue reduction (7).

One of the factors associated with fatigue in RA may be physical activity: in patients with RA but also in patients with other chronic conditions such as chronic fatigue syndrome (CFS), Sjögren's syndrome, cancer and Parkinson's disease, a higher level of fatigue is associated with a lower level of physical activity (8-11). The role of fatigue and physical activity as 'cause' and 'effect' are unclear, however increasing the level of activity might reduce fatigue in RA (12, 13).

Although it appears that fatigue is severe and prevalent in RA, it may seem that in the general population fatigue is also quite prevalent. Whether in RA fatigue indeed is more severe than in the general population is not clear, although two small studies show that this might be the case (5, 14). In other chronic diseases, notably patients with multiple sclerosis (MS) and in cancer survivors, it has been shown that fatigue was more severe than in the general population (15, 16). Also, physical activity levels (subjectively or objectively measured), are significantly lower in patients with MS, CFS, Chronic Obstructive Pulmonary Disease (COPD) and type-2 diabetes mellitus compared to healthy subjects (8, 17). As fatigue and physical activity are related in several chronic diseases, the level of physical activity in RA patients might also be relevantly lower compared to the general population.

In the past, several studies compared physical activity levels of RA patients and healthy controls, and demonstrated that the level of physical activity is lower in RA patients (1, 14, 18, 19). It may be of value in the management of RA to promote physical activity, for instance to reduce fatigue (12, 13, 20, 21). Besides that, physical activity has several other beneficial effects for people with RA, such as reduction of cardiovascular risk, increasing aerobic capacity, increasing muscle strength, and reducing pain and disability (12, 22-24). To update the information about fatigue and physical activity in RA patients compared to the general population and to collect information about how many RA patients and people of the general population comply to the recommendation of moderate-intensity aerobic physical activity for a minimum of 30 minutes on at least five days each week ,(1) we performed this study. In addition limitations to begin with a new

sport are assessed which may be helpful for the development of an activity program to treat fatigue in RA.

The objectives of this study were 1) to compare the level of physical activity and the level of fatigue between RA patients and the general Dutch population and 2) to investigate whether self-reported physical activity depends on age, gender, BMI, and disease duration in RA patients, and 3) to describe which sport activities RA patients perform and which limitations RA patients experienced to participate in sports.

## Methods

### Design

Three different study populations were used: two RA populations and one sample from the general population.

The first patient population consisted of 228 RA patients who visited the outpatient clinic of the Radboud university medical center at Nijmegen in 2006 and 2007. Information about patient characteristics and fatigue was collected using questionnaires that were filled out by the patients in 2006 and 2007.

The second study population consisted of 771 RA patients who filled out an online questionnaire between April 2013 and October 2014. Patients had been invited via 1) the website of the rheumatism foundation in the Netherlands and via a patient magazine and a newsletter especially for people with rheumatism, or 2) via their online electronic patient database called Rheumatology Online Monitor Application (ROMA). The questionnaire consisted of questions about patient characteristics (age, gender, BMI, disease duration) and physical activity (Short QUestionnaire to Assess Health enhancing physical activity (SQUASH)) and the RSO (the guideline for sport participation) about sport habits.

Data from the general Dutch population were obtained using a subset of participants from the Nijmegen Biomedical Study (NBS). Details of the NBS have been described before (25). Briefly, the NBS is a population-based survey conducted by the Department for Health Evidence and the Department of Laboratory Medicine of the Radboud university medical center. In 2002, 22451 age and sex stratified randomly selected inhabitants of the municipality of Nijmegen received an invitation to fill out a postal questionnaire (NBS-1), including questions about lifestyle, health status, fatigue (Shortened Fatigue Questionnaire (SFQ)), and medical history, and to donate an 8.5 ml blood sample in a serum separator tube and a 10ml EDTA blood sample. A total of 9350 (43%) persons filled out the questionnaire, of which 6468 (69%) donated blood samples. After NBS-1, several additional NBS phases were initiated (NBS phase 2 to phase 5) in which participants of each phase were re-invited to participate in the next phase, provided that they did not object against participation in follow-up studies. In the current study, we included 3833 participants from the NBS that completed both the NBS-1 (including questions on fatigue; 2002) and NBS-5 (including questions on physical activity based on the SQUASH questionnaire; 2012).

### Fatigue

In the NBS, fatigue was assessed using a short version of the fatigue severity subscale of the Checklist Individual Strength (CIS20), the Dutch 'Shortened fatigue questionnaire' (SFQ) (26, 27). The SFQ consists of the following four items, each

of which is scored using a 7 point Likert scale: 'I feel tired', 'I tire easily', 'I feel fit' and 'I feel physically exhausted'. The SFQ has shown good internal consistency (Cronbach α=0.88) and was found able to discriminate between patients and healthy subjects (27). The total SFQ score has a range between 4 and 28, whereby a higher score of the SFQ indicates a more severe level of fatigue.

In both RA populations, fatigue severity was measured using the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS20) (26). 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. The SFQ score was calculated from the 4 items of the CIS20, as described above.

**Physical activity**

Physical activity was assessed using the SQUASH for both RA patients as for the general Dutch population. This Dutch questionnaire is a reliable and valid method to measure physical activity during one week (28). It contains ten questions divided over four categories: commuting, activities at work or school, household activities and leisure time activities. The respondents were asked to refer to an average week in the last month. Total amount of physical activity in minutes per week was calculated by multiplying the average time per day for each activity with its days per week, followed by summing the time per week of all the four categories. In addition, the percentage of persons who fulfill the recommendation for daily physical activity was assessed. This recommendation from the American College of Sports Medicine and the American Heart Association recommended that all healthy adults aged 18 to 65 years need moderate-intensity aerobic physical activity for a minimum of 30 minutes on at least five days each week (1).

The questionnaire filled out by the RA patients also contained the RSO (the guideline for sport participation) about sport habits. This standardized questionnaire consists of questions about sport frequency, the type of sport, the options for activities in the near environment, and the type of sport club. Furthermore, it contains questions about any activity restriction, advice regarding sports, history of exercise and possible interest in type of sport (29).

**Statistical analysis**

All variables were tested for missing values and outliers. An outlier was defined if the z-score of the absolute value > 3.29 and were imputed by single imputation. Single imputation was performed based on multiple linear regression for replacing missing values. Differences in age, gender and body mass index (BMI) between RA patients and the general Dutch population were analysed using an independent student t-test (continuous variables) or a Chi-square test (categori-

cal variables) as appropriate. Differences in fatigue scores between both groups were tested using a Mann-Whitney U test. Differences in total physical activity in minutes per week were tested between both groups using a Mann-Whitney U test. Linear regression was performed in RA patients with physical activity as dependent variable and age, gender, BMI and disease duration as independent variables to investigate whether self-reported physical activity depends on these variables. Variables and residuals were tested for normality. Analyses were performed with SPSS, version 20.0 (SPSS, Chicago, IL). Results are presented as median plus interquartile ranges unless stated otherwise.

## Results

Of the 771 RA patients who started the online questionnaire, 740 RA patients filled out the questionnaire completely. The Nijmegen Biomedical Study (NBS) received 3833 questionnaires from the respondents who were invited in 2012 to fill out the NBS-5 questionnaire (response rate NBS-5 51%). Of these 3833 NBS participants who filled out questionnaires NBS-1 and NBS-5, 3764 participants were included in this study, because they completed questions on fatigue (NBS-1) and physical activity (NBS-5).

**Table 1.** Characteristics of the study population*

| | | **RA patients n=740** | **General Dutch population n=3764** | **P-value** |
|---|---|---|---|---|
| **Patients characteristics** | Age, years, mean ± SD | 55.9 ± 11.5 | 52.1 ± 15.2 | <0.001* |
| | Female, number (%) | 409 (55) | 2025 (54) | 0.488 |
| | Body mass index, kg/m$^2$ , mean ± SD | 26.2 ± 4.7 | 25.0 ± 3.9 | <0.001* |
| **Physical activity in hours/week (SQUASH)** | Total physical activity | 24.6 (11.9-40.5) | 33.0 (16.0-50.0) | <0.001* |
| | Commuting activities | 0.0 (0.0-0.08) | 0.0 (0.0-1.5) | <0.001* |
| | Activities at school or work | 0.0 (0.0-20.0) | 0.0 (0.0-24.3) | 0.020* |
| | Household activities | 6.0 (0.7-14.0) | 8.0 (3.0-16.0) | <0.001* |
| | Leisure time activities | 5.5 (2.9-9.9) | 7.3 (3.0-13.1) | <0.001* |
| **Sport participant** | Number (%) of sport participants | 438 (59.2) | 1980 (52.6) | 0.001* |
| | Number of hours/week | 2 (1-3.8) | 3 (1.5-5) | <0.001* |
| **Physical activity norm** | Activity days/week | 5 (2-7) | 5 (3-7) | 0.207 |
| | Meet physical activity norm, number (%) | 383 (51.8) | 2045 (54.3) | 0.214 |

*Values are median plus interquartile ranges unless stated otherwise. *Significant at P ≤ 0.05

### Patient characteristics

Patient characteristics of the included RA patients and the general Dutch population are shown in Table 1. RA patients are slightly older and have a higher BMI

than the NBS subset, but the percentage of woman is similar. The median (IQR) disease duration of RA patients was 8 years (4-19).

**Fatigue**

RA patients experienced significant ($p<0.001$) higher levels of fatigue (Figure 1) with a median score of 16 (11-22) on the SFQ compared to the general Dutch population who had a median SFQ score of 9 (6-15).

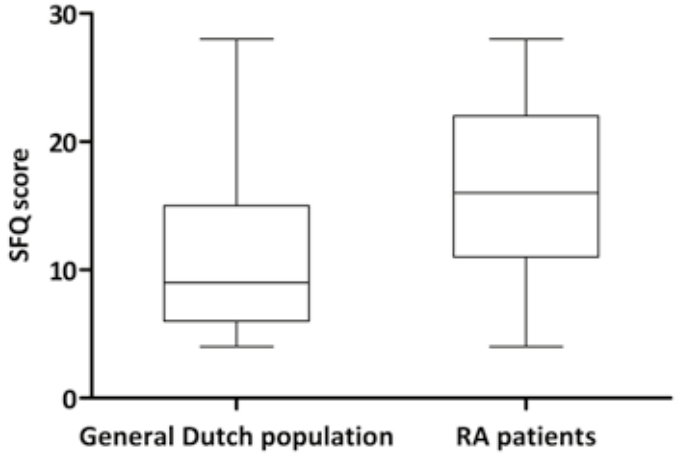


**Figure 1.** Box plots of the SFQ score for fatigue are shown for the RA patients and the general Dutch Population (NBS subset). The bold horizontal bars indicates the medians, the end of the boxes indicates the quartiles. Whiskers indicates minimum and maximum values.

**Physical activity**

Overall, the percentage of missing values of the physical activity questions was low in the dataset: less than 7.1 % of the SQUASH questions were missing in the NBS data and less than 2.2 % for the RA patients. Total physical activity, commuting activities, activities at school or work, household activities and leisure time activities were imputed by age, gender, BMI and not missing SFQ values. The missing SFQ values were imputed by age, gender and BMI and the not missing values of total physical activity, commuting activities, activities at school or work, household activities and leisure time activities.

With respect to the total amount of physical activity, RA patients were significant less physically active compared to the general Dutch population, with a median of 24.6 (11.9-40.5) and 33.0 (16.0-50.0) hours per week respectively ($p<0.001$). RA patients spent less time per week in all four categories of physical activity (Table 1). At least once a week, 59% of the RA patients participated in sport, compared to 53% of the general Dutch population ($p<0.001$). However, the

RA patients who participated in sport, spent significant less minutes per week in sport participation compared to the general Dutch population, 120 (60-225) and 180 (90-300) minutes per week respectively ($p<0.001$).

The median number of activity days, a day during which someone participate at least 30 minutes in moderate-intensity aerobic physical activity, is equal in both groups (5 (2-7) days in RA patients and 5 (3-7) days in the general Dutch population, $p=0.207$). Consequently, the percentage of people who meet the international guideline for physical activity did not differ in both groups (51.8% versus 54.3%, $p=0.214$). In RA patients, a lower level of physical activity was related to an older age ($\beta=-0.267$, $p<0.001$) and a longer disease duration ($\beta=-0.167$, $p<0.001$). There was a trend towards a higher BMI level ($\beta= -0.070$, $p=0.058$). Gender ($\beta= -0.009$, $p=0.817$) was not significantly associated with the level of physical activity.

**Sport habits of RA patients**

From the 740 RA patients who filled out the SQUASH questionnaire completely, 708 RA patients also filled out the RSO. At least once a week, 59% of the RA patients participated in sport with fitness, swimming, strength training and walking as the most popular sports. Of the 41% of the RA patients who did not participate in a sport most frequently mentioned reasons were: limitation in physical functioning, dependent on transport, lack of supervision of an expert.

Only a small part of the patients experienced difficulties in participating in sport (6.8%). 38.2% of the RA patients filled out that they had received advise to start participating in a sport. Advice was most frequently given by medical specialists, followed by physiotherapists and general practitioners. Of the RA patients, 32% has interest to practice a new sport. However, most frequently mentioned limitations to begin with a new sport are physical impairment, not being aware of the options, and fear of injuries.

## Discussion

According to the results of this study, RA patients showed lower levels of physical activity and higher levels of fatigue than the general population; the level of physical activity decreased with age and disease duration while there was no gender difference. At least once a week, 59% of the RA patients participated in sport with fitness, swimming, strength training and walking as the most popular sports.

RA patients were about eight hours per week less physically active compared to the general Dutch population; RA patients indicated to be physically active for 25 hours a week on average, while this was 33 hours per week for the general population. Interestingly, both half of the RA patients (52%) and half of the people from the general population (54%) were meeting the physical activity recommendation (1).

The fatigue levels were significantly and considerably higher in the RA sample than in the sample from the general population. The SFQ however does not have a cut point for 'severe' fatigue as the CIS has (8). Therefore, we can say that RA patients have more fatigue than the general population, though it is difficult to say how many people have severe fatigue.

Among RA patients who performed sports activities (50%), fitness training, swimming, strength training and walking were most frequently performed and appear to be most popular. Running, cycling and team sports were infrequently engaged in. Of the included RA patients, 32% have interest to practice a new sport. However, most frequently mentioned limitations to begin with a new sport are physical impairment, not aware of the options, and fear of injuries.

These finding are according to a qualitative study about perceptions of the effects of exercise in RA patients (30). The results of physical activity level in this study are in line with those found in previous studies (14, 18, 31-34). When comparing the level of subjectively assessed physical activity between RA patients and controls, it appears in all studies that patients with RA show a lower level of physical activity compared to the control group(14, 31-34). Questionnaires were used to assess physical activity level. Objective assessment of physical activity level, e.g. using activity trackers, has its advantages above subjective assessments e.g. using questionnaires. However, objectively assessed physical activity has not been compared directly between RA patients and controls. When comparing different studies using objective assessment of physical activity level, it appears that indeed patients with RA are less physical active than the general population and more active than people with CFS (35).

There is one previous survey (2007) similar to ours, in which physical activity level was subjectively measured using the SQUASH in 252 patients with RA, com-

pared with reference values from the general population in The Netherlands (18). Fatigue however was not assessed. Regarding physical activity, similar results were found, including the finding that about half of the patients with RA and people from the general population fulfilled physical activity recommendations (18).

Concerning fatigue levels, two smaller previous studies compared self-reported fatigue in RA patients with healthy controls and found significantly higher fatigue scores in patients with RA (5, 14). Fatigue was measured with the Fatigue Severity Scale (FSS) and with the Multidimensional Assessment of Fatigue (MAF), so results cannot be compared. However, it seems a consistent finding that RA patients are more fatigued than the general population. Few studies assessed sport participation and preferences of sports activities in RA (36-38). Differences were found in percentage of RA patients performing sport activities and a comparison between these studies cannot be made because of the different criteria of being physically active or being a sport participant (36-38). Most RA patients preferred exercising at home, alone, at moderate intensity, and the preferred type and most common type of exercise was walking (37).

A limitation of this study was that fatigue was assessed differently in the study populations that we compared. In the general population the SFQ was used for assessing fatigue, which was not available in the RA population. To compare fatigue levels in the general population with fatigue levels in the RA population we used data of another study population including RA patients of our medical center. However, no differences regarding patient characteristics were found between the two RA study populations, thus we assume that the smaller RA population is representative of the larger populations. Secondly, the proportion of females in the RA study population assessed for physical activity was about 50%, similar as in the general population, but usually the proportion of females in RA samples is 60%-80%. Gender was not associated with physical activity level so we regard that the results are generalizable tot other RA study populations.

While patients with RA have more fatigue and a lower level of physical activity, the question remains whether and how physical activity and fatigue are related: is there a causal relation and does one cause the other, or vice versa, or does both happen? In our previously performed study, we showed that the level of fatigue and the level of objectively assessed physical activity in RA are associated: RA patients with more fatigue were less physically active (35). Hypothetically, to break a vicious circle, increasing exercise could be effective to reduce levels of fatigue. Only one single RCT has been performed on aerobic exercise in RA with fatigue as dedicated primary outcome measure (20). In a meta-analysis, the results of this RCT (20) combined with the results of four other RCT's in which fatigue was measured but originally not reported (13), it is shown that an

aerobic exercise program is effective in reducing fatigue among patients with RA (13). However, the effects were small, and further research should be performed to make the evidence more clear. There is some evidence for several forms of activity or exercise that they may be effective in reducing fatigue in RA reported in meta-analysis (12, 21). There however is no evidence to prefer one mode of exercise over the other, nor is it clear what would be the most effective mode to deliver these interventions as well as how best to incorporate exercise into the lives of RA patients (39). Moreover, there are serious concerns about the degree of adherence to long term exercise (39, 40). To facilitate initiation of and adherence to exercise, it is important to understand the perceptions of RA patients and health professionals about barriers and facilitators to exercise (30). These patient perceptions have also been studied using qualitative research and a survey (30, 37). It was found that the most relevant patient perceptions regarding exercise are: 'Health professionals showing a lack of exercise knowledge', 'Not knowing what exercise should be done', 'Nothing can be done about managing fatigue', 'Not wanting to exercise as joints hurt', 'Worry about causing harm to joints' and 'Having to exercise because it is helpful'. Therefore, a patient-individualized exercise program could be a promising treatment for fatigue in RA.



If, in future, exercise also has proven to be effective for fatigue in a trial setting, physical exercise can be implemented by a guideline for the inter-disciplinary treatment of fatigue in RA. For improving aerobic capacity, exercising should be performed between 50-90% of maximal heart rate according to the American College of Sports Medicine's guideline (41). And, as aerobic capacity is a very central concept of physical fitness/human performance, there is good reason to hypothesise that improving aerobic capacity may reduce fatigue. As shown that supervised programs are more effective for inducing a significant improvement in aerobic capacity than home aerobic exercise (42, 43), and factors related to inactivity in RA were reduced self-efficacy for exercise (44), fear avoidance (45), lack of strong motivation (46, 47), we advise to bring patients to a certain level of aerobic conditioning by a short intensive phase of a supervised/coached exercise program. After the supervised exercise program, patients can maintain exercising using their preferred modes of exercise, such as (Nordic) walking, exercise at home, but also exercise at a regular sports center, exercise supervised by a therapist, or on an individual basis with an individual exercise program.

In conclusion, this study showed that the amount of minutes of physical activity per week was lower in RA patients compared to the general Dutch population. In RA, a lower level of physical activity was associated with older age and longer disease duration. The most preferred mode of sport participating in RA was fitness, swimming, strength training and walking. Most frequently mentioned limitations to begin with a new sport are physical impairment, not being

aware of the options, and fear of injuries. In addition, patients with RA reported a higher level of fatigue than the general population. First steps can be taken to develop an effective exercise program to treat fatigue in RA. RA patients should be encouraged to increase physical activity with as consequence a possible reduction in fatigue. Because adherence is a concern and the most effective mode is unclear, in future, a study of exercise for fatigue in RA patients having fatigue should be performed, using a coached graded activity program with continuous monitoring and feedback e.g. by using a commercially available activity tracker.

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# Chapter 5

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

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## 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 behavioral 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 hypothesized 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.

## 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, anemia and depressive disorder have long be held responsible for fatigue in RA. However, the prevalence of anemia 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, catastrophizing 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 co-morbidities 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 metastasized 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 hemoglobin level, and disease activity was assessed by the rheumatologist or a specialized rheumatology nurse, by using the disease activity score (DAS28). Fatigue was collected at baseline using a patient questionnaire. The following psychosocial and behavioral variables that might influence fatigue were collected: mood disturbance, sense of control over fatigue, poor sleep quality and physical functioning by using patient questionnaire.

### Fatigue

Fatigue severity was measured using the fatigue severity subscale (CIS-fatigue) of the Checklist Individual Strength (CIS20) (27). 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, 27). The internal consistency of the CIS-fatigue severity subscale by Cronbach's alpha was 0.88 (27). 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 (28).

**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 (29), (range 0-100) with higher scores indicating less pain. Cronbach's alpha was 0.86 (28).

**Physical functioning**

Physical functioning was assessed using the SF-36 subscales physical functioning and role functioning (29). 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 (28).

**Mood disturbance**

Self-reported depressive symptoms were assessed with 16 statements of the Symptom Check List 90 (SCL90) (30). 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 (30).
Anxiety was assessed with 10 statements of the Symptom Check List 90 (SCL90) (30). 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 (30).

**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 (31) ranges between 7-28. Higher scores on the SES indicate more self-efficacy. Cronbach's-α ranges between 0.68 and 0.77 (32, 33). Helplessness of fatigue was assessed with the subscale helplessness of the Fatigue Catastrophizing Scale (FCS). The FCS is the same questionnaire as the Pain Catastrophizing Scale, (34) 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-α 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) (30). The SCL90 consists of a 5-point Likert scale. Total score ranges between 3-15 with higher scores indicating more sleep problems. Cronbach's- α was 0.80 (30).

**Statistical analyses**

To test for differences between non severely fatigued patients (CIS-fatigue <35) and severely fatigued patients (CIS-fatigue ≥ 35 ) (based on Vercoulen (27)), a chi-square test, unpaired t-test or a Mann-Whitney U test was used as appropriate (Table 1). Structural equation modeling (SEM) is a statistical technique for testing hypothesized 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 (Figure 1). The model was assessed using multiple fit criteria: the comparative fit index (CFI), the standardized 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 minimize the rates of type I and type II error (35, 36). 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 (36). The explained variance of the latent variable fatigue was analyzed by the R squared measure of goodness of fit.

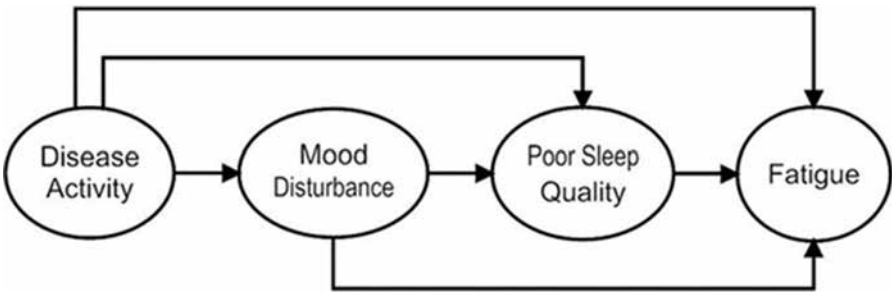


**Figure 1.** NICASSIO P. M. et al: A Multidimensional Model of Fatigue in Patients with Rheumatoid Arthritis. J Rheumatol. 2012; 39(9): 1807–1813

After testing the model of Nicassio (24) in our data, a hypothesized model for fatigue was further developed (Figure 2). This hypothesized 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 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 (37). We therefore included these variables for RA fatigue in our hypothesized 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 (Figure 2). Analyses were performed using SPSS 20.0 and MPlus (version 6.0).



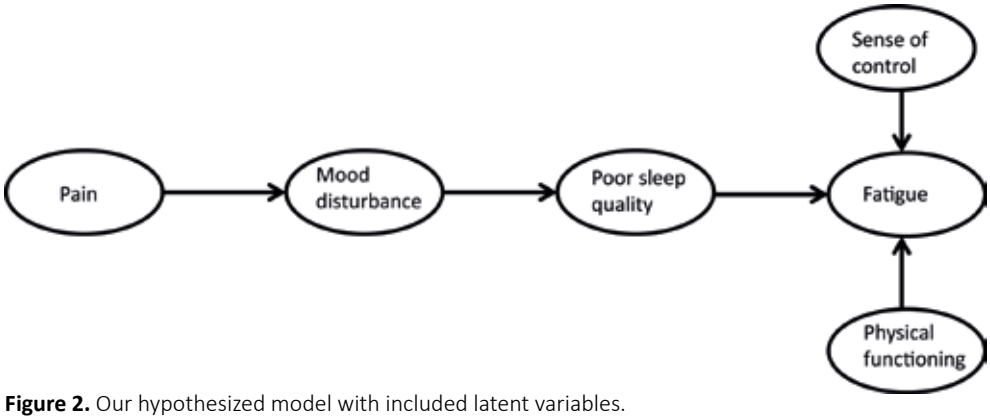


**Figure 2.** Our hypothesized model with included latent variables.

## 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 1). The mean age was 55.9 years, 63% was female and overall the majority had a low disease activity and a moderate fatigue level (27). At baseline, 36% received a tumor 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 1).

**Table 1.** 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, women (%) | 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 |

| | Variables | All patients (n=228) | CIS-fatigue < 35 at baseline (n=132) | CIS-fatigue ≥ 35 at baseline (n=96) | P-value |
|---|---|---|---|---|---|
| | 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 antirheumatic 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 Catastrophizing Scale.

## 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 hypothesized 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 hypothesized 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 standardized correlation coefficients and Table 2 the unstandardized and standardized 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 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.

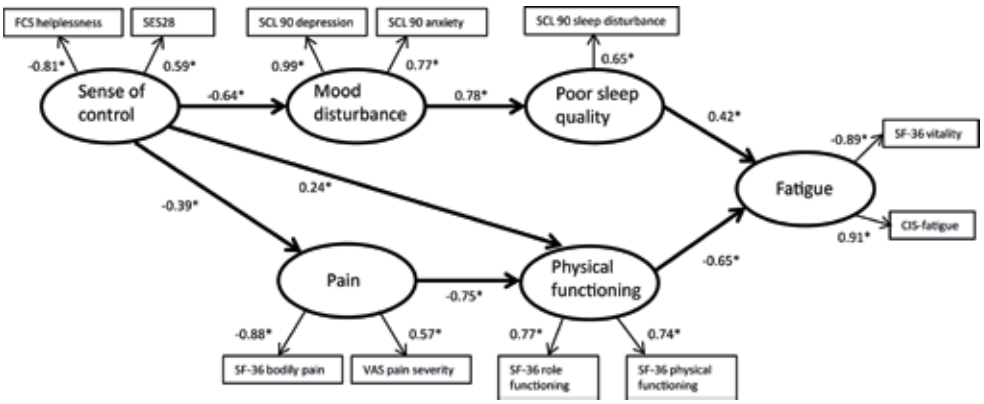


**Figure 3.** The final model with standardized correlation coefficients. SF-36: Short Form Health Survey 36, SCL-90: Symptom Check List 90. VAS: visual analogue scale, CIS: Checklist Individual Strength. * p<0.001. The latent variables are shown in rounds and the constructs of the latent variables are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

**Table 2.** Path coefficients of the final structural equation model*

| Effects | Unstandardized | SE | P-value | Standardized |
|---|---|---|---|---|
| **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 |

*Unstandardized means that the coefficients are uncorrected for differences in scaling. SE: standard error. Standardized means that the coefficients are corrected for scale differences to facilitate comparison.

## 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, 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 analyzed 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 randomized 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 generalization, 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 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 anti-rheumatic medication and pain-medication (38). 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, 39). Stimulus control instructions, and sleep restriction have proven to be effective in other sleep-disordered populations (40, 41). Little has been reported on the effectiveness of CBT in reducing sleep disturbances in patients with RA (42) although a study found improvements in subjective sleep quality after CBT (43). A recent yet incompleted trial is investigating the effect of intermittent aerobic exercise on the improvement of sleep in patients with rheumatoid arthritis (44), however the effect is not known yet.
Alternatively, an exercise program to increase the level of physical activity (functioning) could be effective in reducing fatigue. Several RCT's 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 RCT's, are needed to test the efficacy of these interventions.

**Acknowledgements**
Figure 1 was reprinted from Nicassio et al. J Rheumatol. 2012;39(9):1807-13 with permission of Journal of Rheumatology.

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# Chapter 6

# The effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis

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## Abstract

### Objective

Rheumatoid arthritis (RA) fatigue is not being well-managed currently and evidence about effective interventions is limited. Aerobic exercise may provide benefit to treat fatigue in RA. Therefore, the purpose of this meta-analysis is to analyze the effect of aerobic land-based exercise on fatigue in RA.

### Methods

A literature search was conducted using Pubmed, Cochrane library, Embase and trial registers to identify randomized controlled trials (RCTs) with a supervised land-based aerobic exercise program performed with an intensity between 50-90% of maximal heart rate, of at least 15 minutes duration, performed at least 2 times a week, and lasting for a time period of at least 4 consecutive weeks. Risk of bias was assessed using the Cochrane tool. Meta-analysis of fatigue outcomes was performed by calculating the standardized mean difference (SMD) using a random effects model.

### Results

Five RCT's could be included. None of the trials selected patients with RA for having fatigue. Risk of bias was low in three RCTs and unclear in two. Land-based aerobic exercise programs had a positive effect on fatigue in RA compared to no exercise at 12 weeks, SMD (95%CI) =-0.31 (-0.55,-0.06). At 24 weeks, the effect of aerobic land-based exercise was smaller and not statistically significant, SMD (95%CI)=-0.15 (-0.33, 0.02).

### Conclusion

There is evidence with low risk of bias that an aerobic exercise program is effective in reducing fatigue among patients with RA, especially in the short term, however effects are small. To substantiate the evidence, RCT's should be performed in patients with RA selected for having fatigue.

## Introduction

In rheumatoid arthritis (RA), fatigue is a frequent complaint, even among patients with low and moderate levels of disease activity (1, 2). As much as 40% of the patients with RA may be severely fatigued, having fatigue levels similar to patients with the chronic fatigue syndrome (CFS) (1). Indeed, fatigue in RA is a patient-relevant complaint: patients with RA express their fatigue as unpredictable, overwhelming and different from normal tiredness (2) and it is often perceived as debilitating and restricting daily functioning (1, 3-5). Potentially, fatigue in RA has a large impact on quality of life and patients give high priority to reduce fatigue (6). RA fatigue is associated with multiple factors: disease related factors (pain, joint damage, disability), cognitive and behavioral factors (anxiety, depression, illness beliefs and stress) and personal factors (work/caring responsibilities, environment, health, lost social support) (7).

However, currently RA fatigue is not being well-managed. Lack of knowledge about the causes of fatigue as well as lack of knowledge of effective treatments may contribute to fatigue being neglected during patient-physician contacts (2, 8). Most rheumatologists pay attention to fatigue during the first consultation and less often during follow-up consultations (8). Clinicians may tend to assume that the patient will raise the issue. Having effective interventions for the treatment of fatigue in RA is of major importance, but evidence regarding effective interventions still is limited. Similar to the CFS (9, 10), in RA most evidence is available for the effectiveness of cognitive behavioral therapies (CBT) and exercise (11-16).

The underlying mechanism of fatigue in RA is not known. Previous research supports that psychological factors, pain, physical activity, but not the level of inflammation are related to fatigue in RA (7, 17, 18). Physical functioning as well as activity level may play a role in maintaining fatigue levels in RA (19); a higher level of daily physical activity was associated with reduced levels of fatigue. It is well known from several randomized controlled trials (RCT) in RA that short-term and long-term exercise programs are beneficial to reduce pain and disability and that exercise can be performed safely (20). However, regarding fatigue the evidence is less clear. Systematic reviews indicate that there is evidence to suggest that several exercise forms provide benefit to treat fatigue in RA (15, 16). As aerobic capacity is a very central concept of physical fitness/human performance, there is good reason to hypothesise that improving aerobic capacity may reduce fatigue. However, only one single RCT has been performed on aerobic exercise in RA with fatigue as dedicated primary outcome measure (14). In that trial, fatigue decreased significantly for the exercise group compared to the control group (14). To summarize the limited evidence of the effect of an aerobic

exercise program on fatigue and to get a better estimate of the mean effect, we performed the current meta-analysis. The purpose of this meta-analysis of RCTs was to analyze the short-term (≤12 weeks) as well as the long-term (24 weeks) effect of land-based aerobic exercise programs on fatigue in RA, including published and unpublished fatigue data. In addition, the relation between the effect of the intervention and baseline fatigue and the relation between the effect of the intervention and disability were analyzed.

## Methods

### Design

A literature search was conducted using the electronic databases Pubmed, Cochrane library, Embase and three trial registers to identify RCTs comparing aerobic exercise versus no exercise in RA, regardless of whether fatigue outcomes were published. All authors were approached with a request to provide data on fatigue. Risk of bias of each RCT was assessed using the Cochrane Collaboration's tool for assessing risk of bias (21). Meta-analysis of fatigue outcomes was performed by calculating the standardized mean difference using a random effects model.

### Inclusion criteria

RCT's were included if the following inclusion criteria were met: 1) inclusion of patients with RA according to the ACR classification criteria; 2) supervised land-based (bicycle or running or circuit training) aerobic exercise program; 3) the intervention is between 50-90% of maximal heart rate according to the American College of Sports Medicine's guideline for improving aerobic capacity (22); 4) training sessions were at least 15 minutes for at least 2 times a week, during at least 4 consecutive weeks (22); 5) the study was randomized; 6) the control group did not perform exercise. Supervised land-based aerobic exercise was chosen as an inclusion criteria because this includes most established aerobic training methods that are easy to implement in different forms (cycling, walking, 'aerobics') and training intensity can be well regulated. Generally, supervised programs are more effective for inducing a significant improvement in aerobic capacity than home aerobic exercise (23, 24). Fatigue was not among the inclusion criteria, because we also wanted to include studies in which fatigue data happened to be collected but were not reported.

### Search strategy

A systematic search of Pubmed, Embase and the Cochrane library database was performed in April 2014 for relevant RCTs from 1985 till April 2014, and the search strategies are shown in Table 1.

**Table 1.** Search strategies in Pubmed, Embase and the Cochrane library.

| Database | Search strategy |
|---|---|
| **Pubmed** | ("Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis[all fields]) AND (("Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR exercise*[all fields] OR training[all fields] OR intervention[all fields] OR programs[all fields] OR program[all fields] OR programme[all fields] OR programmes[all fields] OR rehabilitation[mesh] OR rehabilitation[subheading] OR rehabilitation[all fields] OR activity[all fields]) AND (aerobic*[all fields] OR dynamic[all fields])) AND (((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) OR "Meta-Analysis" [Publication Type] OR metaanalysis[tw] OR meta-analysis[tw] OR meta analysis[tw] OR systematic[sb]). |
| **Embase** | 'rheumatoid arthritis'.ti,ab,kw. or rheumatoid arthritis.sh. and (exercise or 'exercise therapy').sh. or exercise.af. or training.af. or intervention.af. or program*.af. or rehabilitation.af. or activity.af. and (aerobic or dynamic).af. Search strategy limited to randomized controlled trials. |
| **Cochrane** | "rheumatoid arthritis" OR Arthritis, rheumatoid [Mesh] AND exercise [Mesh] OR exercise therapy [Mesh] OR exercise OR training OR intervention OR program OR programme OR rehabilitation OR activity AND aerobic OR dynamic. Search strategy limited to trials. |

Further, the clinical trial registers at www.clinicaltrials.gov and www.trialregister.nl and www.clinicaltrialsregister.eu were searched (Figure 1).

### Selection

After screening title and abstract by two of the authors (SR and MF) the articles appearing to be relevant were read full-text and inclusion/exclusion criteria were applied (SR supervised by JF). The first or last authors of all included studies were approached by e-mail to ask whether they had collected any fatigue questionnaires such as the Bristol Rheumatoid Arthritis Fatigue Multi-dimensional Questionnaire (BRAF MDQ), Checklist Individual Strength (CIS20R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy Fatigue (FACIT-F), Multi-dimensional Assessment of Fatigue (MAF), Short Form 36 vitality subscale, or a Visual Analogue Scale of fatigue (VAS), that was not reported in their published article.

### Data extraction

Data on fatigue measures were extracted for the intervention group and the control group, at baseline and follow-up. Standard tables were used for data extraction by one of the authors (SR supervised by JF).

**Study quality assessment**

Two authors (SR and JF) independently assessed the methodological quality of each study using the Cochrane Collaboration's tool for assessing risk of bias (21). The risk of bias tool covers nine items within six domains of bias: selection bias, performance/detection bias, attrition bias, reporting bias and other bias (Table 3). There were 3 rating categories available for each item: 1) low risk of bias: which is unlikely to alter the results seriously, 2) unclear risk of bias: bias that raises some doubt about the results, 3) high risk of bias: bias may alter the results seriously. All selected articles were scored by the two authors. Discordant judgments were resolved by discussion until consensus was reached.

**Analysis**

The effect of an exercise program on fatigue versus no exercise was assessed for each individual study by calculating the weighted standardized mean difference (SMD) and 95% confidence interval of the experimental group versus the control group. Individual SMD of all included studies were pooled using the inverse variance method (25). This was performed for both the short-term (≤ 12 weeks) and long-term (24 weeks) effects of exercise on fatigue. Heterogeneity of treatment effects among studies was statistically investigated using the $I^2$ statistic. The degree of heterogeneity was graded as low ($I^2$< 25%), moderate ($I^2$=25%-75%) or high ($I^2$> 75%) (26). A random effects model was used to pool the studies. Sensitivity analyses were performed regarding risk of bias (low versus other); fatigue data published (yes versus no) and length of supervised part of exercise program (short: ≤ 12 weeks versus long:24 weeks). Meta-regression analyses were performed to analyze the relation between baseline fatigue (standardized as percentage of maximum possible score) and the effect of the intervention (SMD), and to analyze whether there was a relation between the effects on disability (disability index of the Health Assessment Questionnaire) with the effects on fatigue (SMD). In these analyses the RCTs were weighted according to study size. The meta-analyses were done using Review Manager 5 and the meta-regression was performed using SPSS 20.0.

## Results

### Included studies

There were 232 articles identified by the search strategy, of which 86 were duplicates. After screening 146 unique articles on title/abstract, 38 titles were considered relevant for reading full-text (Figure 1). Nineteen studies of the 38 met the inclusion criteria and the other 19 studies were excluded. Reasons for exclusion were: the study was not randomized (9 studies), duration of the intervention was less than 4 weeks (1 study), control group performed any form of aerobic exercise (home-based) (2 studies), intervention was a water-based exercise program (1 study) or strengthening exercise (1 study) or dance-based exercise (not at 50-90% of maximal heart rate) (1 study), the training intensity was not provided (2 studies), the training was not supervised (2 studies).

Of the 19 included studies, only one study reported fatigue as a primary outcome measure (Neuberger 2007). Primary outcomes of the other included studies were disease activity, radiographic damage of the large joints, pain, depression, functional ability, cardiorespiratory fitness, and cardiovascular disease. Three studies were from the same research group (Neuberger) and with the same study population. Consequently, 16 authors were approached and responses were received from 13 authors. In 5 studies fatigue data had been collected and these data were all retrieved (Figure 1).

Also the corresponding investigators of three study protocols found in the trial registers were approached for fatigue data (NCT number: NCT00792675, NCT01553305,NCT01966835). Only one study (NCT01553305) collected fatigue data, but this study was excluded because the control group performed a (self-administered) exercise program.

### Characteristics of included studies

The characteristics of the included studies are shown in Table 2 (14, 27-30). The smallest study included 34 patients (Reid 2011), the largest study (de Jong 2003) included 298 patients.

The interventions included cycling, running or circuit training for at least 15 consecutive minutes with a frequency of 2 or 3 times a week. The length of the supervised training programs differed between 4 weeks (van den Ende 2000) and 104 weeks (de Jong 2003). However, all studies collected fatigue data at 24 weeks after baseline. In three studies the MAF was used as fatigue scale, in one study the SF-36 vitality subscale was used and one study used a VAS fatigue scale (Table 2).

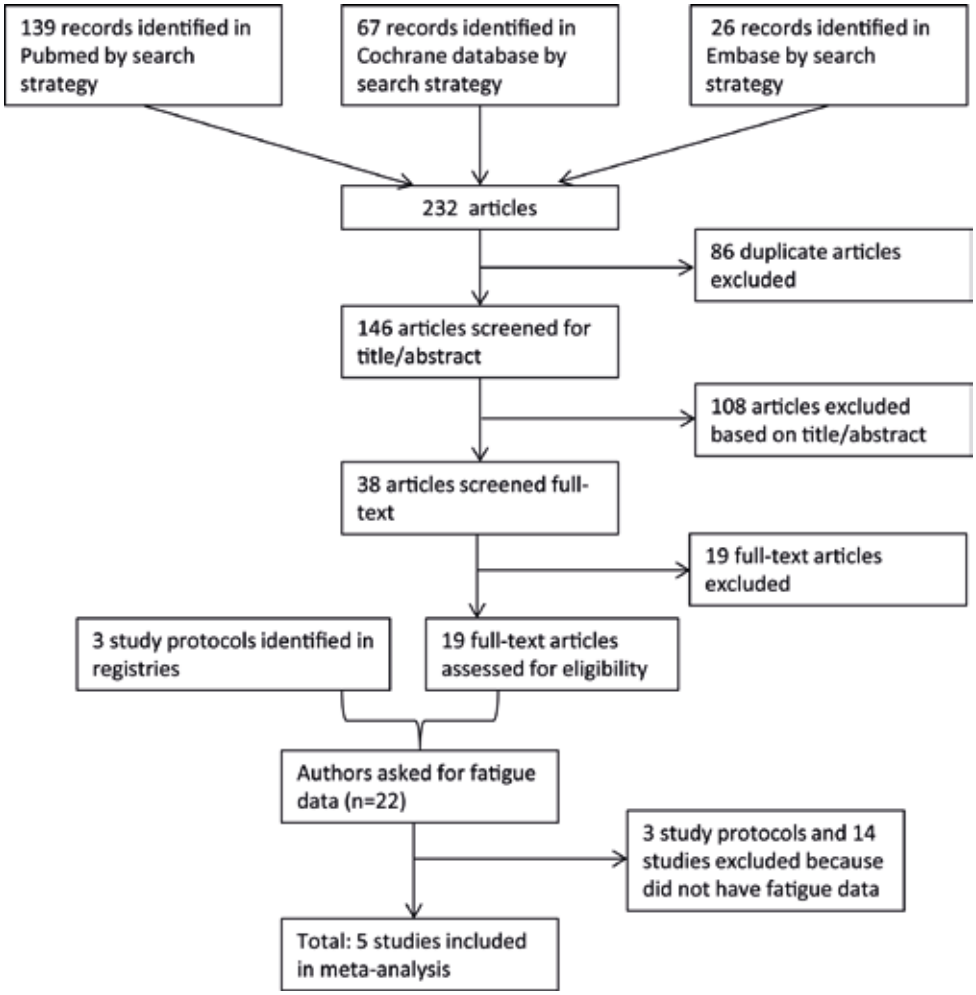



**Figure 1.** Flow chart search strategy

**Table 2.** characteristics of included studies in meta-analysis*

| | N intervention/ control | Fatigue scale | Primary outcome | Baseline fatigue score (mean (SD)) intervention/ control | Exercise type | Adherence | Freq/ week | Intensity | Duration, min | Length, weeks | Control group |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Van den Ende 2000** | 34/29 | VAS fatigue | Disease activity | 5.3 (3.1) / 5.9 (3.2) | Bicycle, muscle strength training | Mean (SD) number of intensive exercise sessions was 16 (9) | 3 | 60% max HR | 15 | 4 | 60% max HR |
| **De Jong 2003** | 149/149 | SF-36 vitality | Radiographic damage of the large joints, disease activity | 56.80 (17.16) / 55.46 (18.6) | Warming-up, 20 min bicycle, 20 min circuit, 20 min sport and game, cooling down | No adherence over time, after 2 years 81% still participate in the exercise class | 2 | 70-90% max HR | 85 | 104 | Usual care |
| **Neuberger 2007** | 67/73 | MAF | Fatigue, pain and depression | 24.91 (10.25) / 21.88 (9.8) | Warming-up, low impact aerobics, strengthening and cooling-down | 83.3% | 3 | 60-80% max HR | 60 | 12 | Baseline amounts exercise |
| **Reid 2011** | 17/17 | MAF | Functional ability | 17.46 (7.81) / 24.87 (9.55) | Land-based: 10 min warming-up, 40 minutes circuit, 10 min cooling-down | 78% | 2 | moderate to vigorous level, | 60 | 8 | no intervention |
| **Stavropoulos –Kalinoglou 2012** | 18/17 | MAF | Cardiorespiratory fitness and cardiovascular disease | 22.82 (10.5) / 23.60 (11.3) | 10 min warming-up, 30-40 main session consisting of walk on treadmill, cycle, row or hand ergometer, 5-10 min cooling down | 88%, 76% | 3 | 70% VO2 max | 50-60 | 24 | Receiving verbal advice on exercise benefits and lifestyle changes |

*VAS= Visual Analog Scale; MAF=Multidimensional Assessment of Fatigue; HR=Heart Rate; SF-36= Short Form health survey 36-item

**Adherence to the exercise program.**

The way adherence was reported differed highly between the included studies. In the study of Van den Ende (29) the mean (SD) number of completed exercise sessions was 16 (9); one patient in the intervention group and one patient in the control group were lost to follow-up at 3 weeks of exercise. In the study of De Jong (28), 118 (81%) patients still participated in the exercise class after 2 years; no other data were reported. Median amount of exercise sessions followed in the class exercise group of the study of Neuberger (14) was 83%. The mean attendance rate for the study of Reid (30) at the 8 week gym group sessions was 78%. At 24 weeks, telephone interviews had been conducted and a large majority of participants (82%) responded that they did not continue with their exercise program, which was mainly attributed to a lack of access to suitable facilities and a lack of motivation (30). Mean attendance rate for the study of Stavropoulos-Kalinoglou (27) was 88% for the training group.

**Study quality assessment**

Blinding of participants and personnel, and blinding of the outcome assessment was not present for the fatigue outcome in any included study, due to the nature of the intervention (exercise) and outcome (patient questionnaire). Therefore, a high risk of performance bias was not taken into account when summing up the domains into the overall risk of bias. Three studies had a low risk of bias according to the Cochrane collaboration's tool, two studies had an unclear risk of bias (Table 3). The percentage risk of bias per item for all included studies is shown in Figure 2.



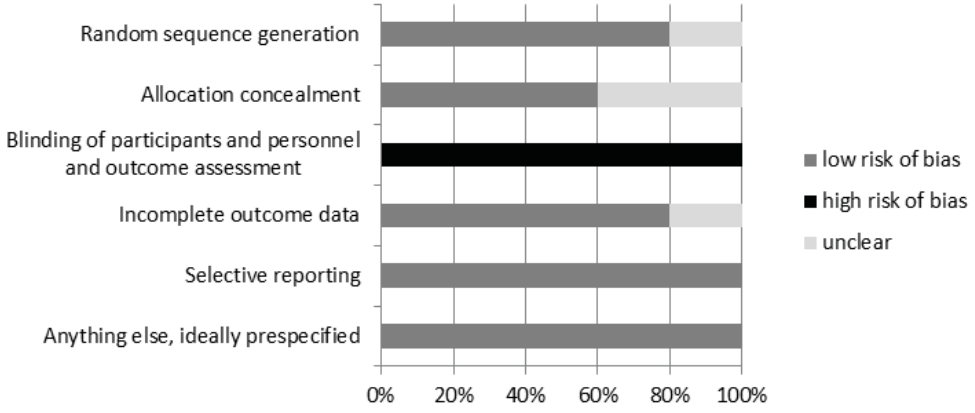



**Figure 2.** Percentage risk of bias per item of all included studies

**Table 3.** Cochrane collaboration's tool for assessing risk of bias*

| Study | Selection bias | | Performance bias | Attrition bias | Reporting bias | Other bias | Total |
|---|---|---|---|---|---|---|---|
| | Random sequence generation | Allocation concealment | Blinding of participants and personnel and outcome assessment | Incomplete outcome data | Selective reporting | Anything else, ideally prespecified | Risk of bias |
| **Van den Ende 2000** |  |  |  |  |  |  | Low |
| **De jong 2003** |  |  |  |  |  |  | Low |
| **Neuberger 2007** |  |  |  |  |  |  | Unclear |
| **Reid 2011** |  |  |  |  |  |  | Low |
| **Stavropoulos –Kalinoglou 2012** |  |  |  |  |  |  | Unclear |

* happy smiley= no; unhappy smiley= yes; neutral smiley= unclear

## Meta-analysis

The short-term effect of exercise on fatigue was calculated using the SMD of the intervention and control group at baseline compared to 4 weeks (Van den Ende 2000), 8 weeks (Reid 2011) or 12 weeks (Stavropoulos 2012 and Neuberger 2007). The long-term effect was calculated using the SMD in fatigue score at baseline compared to 24 weeks (24-week data available for all studies). De Jong et al. (2003) did not collect short-term fatigue data and hence their data were only included in the analysis of effects of 24-weeks of exercise.

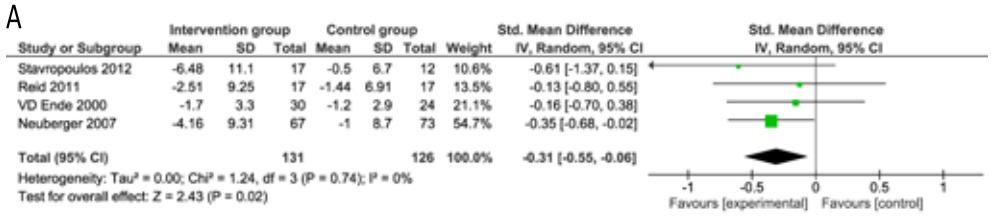
The pooled analysis of the effect of the results at ≤12 weeks of exercise on fatigue revealed a larger reduction of fatigue in the intervention group compared to the control group, which was significant (SMD= -0.31, 95% CI= -0.55;-0.06, p=0.02, $I^2$=0%, (Table 4a)).

The pooled analysis of the effect of 24 weeks of exercise on fatigue also showed a larger reduction of fatigue in the intervention group compared to the control group, however this was not significant (SMD= -0.15, 95% CI=-0.33;0.02, p=0.09, $I^2$=2%,(Table 4b)).

Heterogeneity according to the $I^2$ was low for both the short term and long term results.

**Table 4.** Forest plot of standardized mean difference, with 95% confidence interval (95% CI) for fatigue score.*

A

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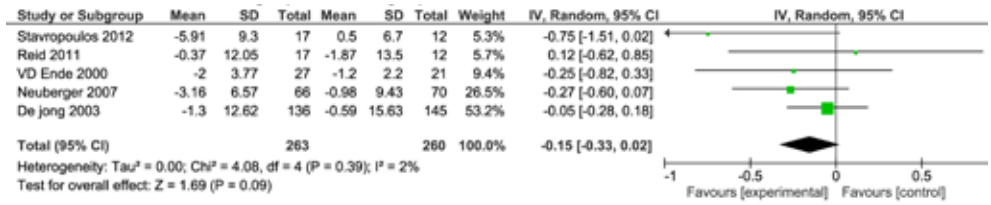


* **4a.** The difference in fatigue score between baseline and 8 or 12 weeks (short-term). **4b.** The difference in fatigue score between baseline and 24 weeks (long-term). IV=inverse variance.

## Sensitivity analyses

When comparing the studies with a low risk of bias (van den Ende 2000, Reid 2011) with the other studies (Neuberger 2007, Stavropoulos 2012), the pooled analysis of the effect of short-term exercise on fatigue showed no effect in the low risk of bias group (SMD=-0.15, 95% CI=-0.57;0.27, p=0.50) but there was a larger and statistically significant effect of exercise on fatigue in the studies with an unclear risk of bias (Neuberger 2007, Stavropoulos 2012) (SMD=-0.39, 95% CI=-0.70;-0.09, p=0.01).

The pooled analysis comparing the study with fatigue as a reported primary outcome (Neuberger 2007) versus all studies which did not report fatigue outcomes in their published article, showed a larger reduction of fatigue in the study of Neuberger (SMD=-0.35, 95% CI=-0.68;-0.02, p=0.04). However, there was no effect of exercise training on fatigue in the pooled other studies (SMD=-0.25, 95% CI=-0.62;0.11, p=0.17).

The only study in which an exercise program longer than 24 weeks was investigated is the study of De Jong 2003, which was a two year supervised high-intensity group exercise program. The effect of the intervention group compared to the control group at 2 years was not significant (p=0.53); the intervention group had a somewhat higher level of fatigue on the SF-36 vitality scale at two years of exercising (+0.77 (15.5)) compared to baseline.

The pooled analysis comparing the studies with a short supervised part of the exercise program (≤12 weeks) (Reid 2011, Neuberger 2007, van den Ende 2000)

versus the studies with a longer supervised exercise program (24 weeks) (De Jong 2003, Stavropoulos 2012) showed a somewhat larger reduction in fatigue (not significant) in the studies with a longer supervised program (SMD=-0.30, 95% CI=-0.95;0.36, p=0.37) than in studies with a shorter supervised program (SMD=-0.21, 95% CI=-0.48;0.06, p=0.13).

**Meta-regression**

In most studies the average baseline fatigue score was similar and ranged between 45% and 55% of the maximum score possible; in one study the level of fatigue at baseline was below 20%. There was no significant relation (Figure 3) between the level of baseline fatigue score and the effect of the intervention on fatigue (β=-0.012 p=0.396, $R^2$=0.25).

The study with the lowest baseline fatigue score is the only study in which the benefit in the control group was larger than the benefit of the intervention group (a 'reversed' effect). If this study is omitted in the meta-regression, the level of baseline fatigue also does not have a significant effect on the intervention effect (p=0.612).

The meta-regression of the relation between the effect on fatigue with the effect on disability/functioning showed that larger effects on disability were associated with larger effects on fatigue (β= 1.04 p=0.027, $R^2$=0.947).

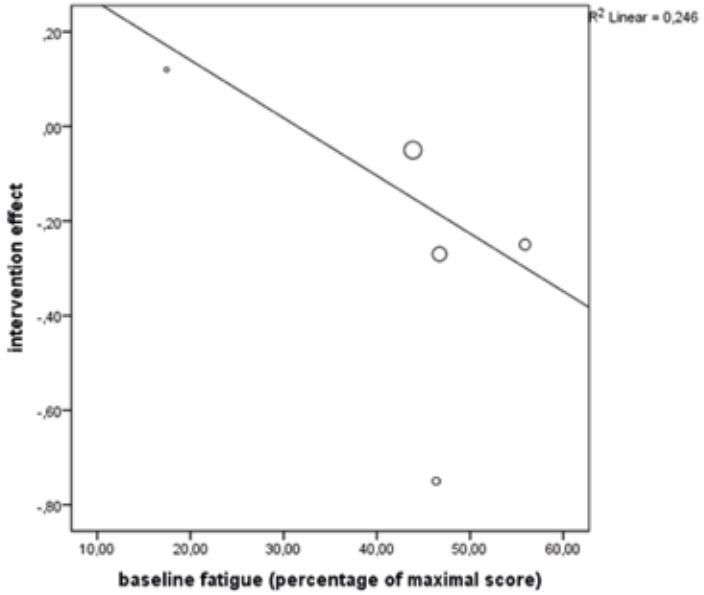


**Figure 3.** Meta-regression of baseline fatigue score and the effect of the intervention

## Discussion

This meta-analysis identified 5 RCT's in which the effect of a supervised land-based aerobic exercise program on fatigue in patients with RA was studied. Accordingly, this analysis showed by pooling the SMD of included studies that aerobic exercise training may be beneficial to treat fatigue in RA. The effect of aerobic exercise on fatigue was highest and statistically significant at 12 weeks, while this effect diminished over time with no significant effect found at 24 weeks.

The 5 included trials were reasonably well performed and accordingly the overall risk of bias was judged as low. The main source of bias, common to all studies, was that the intervention could not be blinded for the patients while fatigue is being measured by patient questionnaire. This cannot be avoided, due to the nature of intervention and outcome. In the individual studies the effects of exercise on fatigue were not statistically significant, with one exception, showing the advantage of meta-analysis if studies are small. However, the effect sizes in the individual studies also were relatively small, usually with a SMD of <-0.5. So far it can be concluded that in these RCTs, the effect of aerobic exercise for fatigue in RA was small at 12 and 24 weeks, with a low risk of bias.

Unfortunately, in the several RCTs different fatigue outcome measures were used. Three of the five included studies used the MAF as fatigue questionnaire (14, 27, 30) and two studies used a different fatigue outcome (28, 29). This necessitated the use of the dimensionless SMD to enable comparison between studies. However, the use of different outcome measures did not cause a lot of heterogeneity. Alas, of the 22 trials included in only 5 were fatigue outcomes assessed (14, 27-30) and in only one study fatigue was reported as the primary outcome measure. Notably, none of the trials selected patients with RA for having fatigue. This may have contributed to the relatively small effect sizes that were found; the effects of an intervention to reduce fatigue may be larger if patients are selected on fatigue levels as indication. While in meta-regression it was shown that in most studies fatigue was present at baseline, there was no indication that the effect depended on baseline level, presumably because the baseline level of fatigue was quite similar for most studies. Also, it could be that the different lengths of the exercise program and the degree of adherence contributed to the small effect size. It is conceivable that a number of participants may not have continued to exercise after the supervised training program was finished. Generally, supervised programs are more effective for inducing a significant improvement in aerobic capacity than home aerobic exercise (23, 24). However, a recently performed RCT showed a significant effect of a home-based exercise program on fatigue (31). Three of the 5 included studies performed a supervised exercise program less than 24 weeks. In our sensitivity analysis a larger

reduction in fatigue in the studies with a longer supervised exercise program was found compared to studies with a shorter supervised part, however not significant. Evidence from meta-analyses and RCT's showed that for CFS, CBT (10, 11) and exercise (9) are effective treatments. Therefore, there is reason to consider CBT and exercise as treatment modalities for fatigue in RA too. However, the factors contributing to fatigue are different in RA as compared to the CFS, with presence of chronic pain in RA as a predominant difference (18, 32). Thus, results in CFS cannot automatically be translated to RA. Regarding CBT to treat fatigue in patients with RA, several RCT's have shown that it is effective, although effect sizes are small (11-13). Regarding exercise, there is some evidence to suggest that several exercise forms provide benefit to treat fatigue in RA, from two meta-analysis (15, 16). However, only one study on aerobic exercise was included in these meta-analyses. Although the evidence is not abundant and effects appear to be small, CBT and exercise appear to be promising interventions for the treatment of chronic severe fatigue in RA. This has also been suggested in patients with primary Sjögrens' disease: fatigue might be reduced by targeting both physical activity and physical activity cognitions (33).

The current meta-analysis concentrates on land-based aerobic exercise and included all currently available evidence including previously unpublished data in RA. Land-based exercise was chosen because this form of exercise is common, easy to implement in different forms (cycling, walking, 'aerobics') and the intensity can be well regulated. Other forms of exercise such as strengthening exercises or a "water based" or dance-based intervention program also could have positive effects on fatigue in RA (15). If the most beneficial intensity of aerobic exercise to treat RA fatigue would be known, clinicians could provide this guidance to patients. If exercise has proven to be effective in a trial setting, physical exercise can be implemented by a guideline for the inter-disciplinary treatment of fatigue in RA, and implementation through patient organizations. For acceptability and adherence it would be advantageous if patients could choose their favorite mode of exercise. Many patients do not want to take part in intensive exercise for a prolonged period of time, therefore a good solution could be to bring the patients to a certain level of aerobic conditioning by a short intensive phase of the exercise program, and use patient preferred modes of exercise for the maintenance phase. One efficient way to train aerobic capacity for instance is cycling, it can be implemented as 'spinning' groups with or without peer-patients in the residential area of the patient and it can also be performed alone and/or at home. However also other exercise modalities can be used, such as (Nordic) walking, exercise at home, but also exercise at a regular sports center, exercise supervised by a therapist, or on an individual basis with an individual exercise program.

In conclusion, the current meta-analysis provided evidence that there may be a positive effect of a supervised aerobic exercise program on fatigue in RA, but the effect was small and non-significant at the long term. However, patients in these studies were not selected for having fatigue and therefore the effect may have been underestimated. For future research, we recommend performing a randomized study on the effects of exercise in patients with RA with fatigue as main outcome, in patients selected on high fatigue levels. In future, patients should be supported to continue the exercise program beyond the supervised part of the program, aiming to establish a better effect on the longer term. This could be performed by an internet-based individualized training even in combination with group contact moments (34, 35). In addition the optimal dose and frequency of exercising to establish an effect on fatigue in patients with RA is yet unknown and should be studied. Further it would be an advantage if a common fatigue outcome measure, such as the MAF, would be used in future trials, to facilitate meta-analyses. Also, the BRAF (Bristol Rheumatoid Arthritis Fatigue) could be included as an RA specific fatigue questionnaire, probably as a primary outcome measure (36).

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# Chapter 7

## Discussion

## Discussion

Fatigue is an important disturbing symptom for patients with RA and its aetiology still remains unclear. The evidence base for the treatment of fatigue in RA is limited. This thesis was performed with the aim to gain more insight into factors associated with fatigue in RA, and especially to get more insight in the association between physical activity and fatigue. We hypothesized that RA patients with severe fatigue are trapped in a vicious circle: a decrease in physical activity is associated with a higher level of fatigue which may lead to more mood disturbance and less sense of control over fatigue, associated with a further decrease in physical activity, and so on. To get a better understanding of fatigue and to find keys to treat fatigue, it is necessary to clarify the relations between fatigue, physical activity and other factors.

Based on the chapters described in this thesis the main findings are:

- A change of fatigue is positively associated with a change of pain over the same period of time. A synchronous association was found and not a successive relationship. Therefore both pain and fatigue should be treated because it cannot be expected that an improvement in one is followed by an improvement in the other.
- In RA patients, 25% had a low physical activity level, and 75% had a relatively high activity level, as assessed using actigraphy. Patients with RA who had a relatively high level of daily physical activity reported less severe fatigue than patients with lower daily physical activity. Importantly, the level of physical activity was not associated with fatigue related factors: pain, disability, coping, or cognition.
- Patients with RA reported a higher level of fatigue and less minutes of physical activity per week (subjectively measured) compared to the general population. In RA a lower level of self-reported physical activity was associated with older age and longer disease duration. About half of the RA patients reported to participate in sports like fitness, swimming, strength training and walking.
- Testing a hypothesized model of fatigue in RA, fatigue appeared to be influenced directly by poor sleep quality and physical functioning, and indirectly by sense of control, mood disturbance and pain. Changing these factors by psychological interventions and/or physical activity might help to improve fatigue in patients with RA.
- Results of a meta-analysis showed that an aerobic exercise program could be effective in reducing fatigue among patients with RA, especially in the short term, although the effects were small.

Now, the main findings of this thesis will be discussed and implications of the findings will be put forward.

**Factors associated with fatigue**

Formerly, it has been assumed that chronic inflammation and inflammation associated anemia, and thereby depressive disorder were the most important causal factors of fatigue in RA. As chronic inflammation is a catabolic process, it may be hypothesized that inflammation leads to fatigue. However, there are contradicting results between DAS28, ESR, other inflammatory markers and their association with fatigue (1-6). It has been shown in multiple cross-sectional studies that pain, rather than inflammation e.g. as measured using the acute phase reactants or the number of swollen joints, is associated with fatigue in RA (3-5). Consequently, the relation between inflammation and fatigue appears to be mediated through pain (7). Therefore it may be hypothesized that a change in pain may precede a change in fatigue. However, according to the results of this thesis it seems that pain and fatigue have a synchronous association rather than a temporal association. This may suggest that both pain and fatigue are driven by common factors.

Although anemia and depressive disorder do occur in RA, they do not occur so frequently that this can explain the high prevalence of fatigue in RA (8, 9). However, it has been shown that self-reported depressive symptoms are associated with RA fatigue (3, 5, 10-13). Other psychological factors related to higher fatigue in RA are: lower self-efficacy with respect to fatigue (3, 10, 11), a perceived lack of social support (3, 11), lower mental health (6), low self-esteem, catastrophizing of fatigue, strong somatic fatigue attributions, less social functioning and coping strategies like worrying and resting (10). Longitudinal studies assessing fatigue at baseline and after one year, showed that pain, daily functioning, and psychological factors such as self-efficacy and coping strategies are related to fatigue severity in RA (14-16). Physical functioning also is an important variable associated with fatigue in RA: several studies showed that fatigue was closely related to activity limitation (4, 6, 10, 15, 17).

In 2011, Hewlett developed a conceptual model for fatigue in RA which provides an overview of all variables associated with fatigue derived mainly from cross-sectional studies (7). This model suggests bi-directional inter-relationships between and within three major factors: RA disease processes, cognitive/behavioural factors and personal/social factors (Figure 1). Combinations of these factors are likely to vary within and between patients, and subject to changes over time. In addition, a recently performed systematic review including all available evidence about factors associated with fatigue in RA until now, concluded that three variables have a high probability to be involved in the complex

process of fatigue in RA: pain, disability/physical functioning and depression/ depressive mood (18), while more evidence was found for fatigue being related to pain and physical function than to depression.

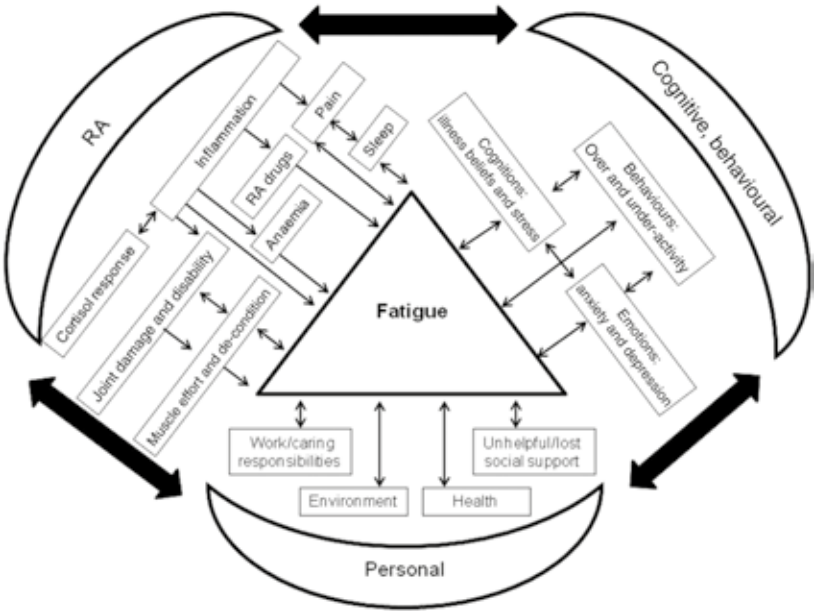


**Figure 1.** Conceptual model of RA fatigue of Hewlett et al. 2011.

Accordingly, these factors seem to be the most important factors contributing to the presence of fatigue. However, it is unknown if these factors are either cause or consequence of fatigue in RA. A causal relationship between these variables and fatigue in RA is difficult to establish, and needs testing in longitudinal observational studies or RCT's with interventions for these factors.

A first step towards how these factors together may contribute to fatigue in RA is by testing a multidimensional model using structural equation modeling (SEM). There was one previous study in which a multidimensional model for fatigue in RA was tested, and a direct relationship between poor sleep quality, mood disturbance, disease activity and fatigue was found (19). Thereby, disease activity was indirectly associated with fatigue via mood disturbance and poor sleep quality. In CFS, also a model for fatigue was developed. CFS is a chronic disorder, different to RA, however in this model cognitive/behavioral factors and physical activity are, like in RA, also associated with fatigue. Therefore, in this thesis, a hypothesized model for fatigue was tested based on the previously developed model for fatigue in RA (19) and on the model for CFS (20). The results of the model developed in this thesis showed that RA fatigue is directly influenced by poor sleep quality and physical functioning, and indirectly by sense

of control, mood, and pain. Besides pain, physical functioning and mood (depressive symptoms) as found in the systematic review of 2013 (18), poor sleep quality seems an important factor contributing to fatigue in RA. Indeed, a recent cross-sectional study about predictors for fatigue in RA showed that besides pain, also depression, physical inactivity and sleep disturbances are associated with a higher fatigue level in RA (21). These combined findings corroborate the viewpoint that these factors are important causal factors of RA fatigue. Therefore, it could be of interest to see whether these four factors are also associated with fatigue in other inflammatory diseases such as ankylosing spondylitis or Sjögren's disease. If these factors are generalizable to all chronic inflammatory disorders at least to some extent, this would facilitate knowledge transfer and evidence based treatments. Interestingly, previous models for fatigue in other, non-arthritic, chronic disorders showed that there may be some common factors indeed: psychological factors, pain and sleep disturbances (22-24). In patients with neuromuscular disorders, a direct relationship between sleep disturbances, self-reported physical activity and fatigue was found (22). Cancer-related fatigue in breast cancer patients was directly associated with depression and anxiety, pain and altered vigilance (23). In multiple sclerosis, higher pain levels were associated with higher levels of fatigue, anxiety, and sleep disturbance, which in turn were associated with higher levels of depression (24).

In conclusion, in RA as well as some other chronic disorders, the most important factors associated with fatigue are sleep quality, mood/depression, pain, and recently also physical functioning was mentioned as a contributing factor (7, 18, 19, 21-24). Physical functioning is a broad concept that reflects patient's impairments, limitations related to movement, and ability to perform daily activities. Physical functioning may be related to, but does not cover, the amount of daily activity a patient performs. Physical activity is defined as any bodily movement resulting in energy expenditure (25), including exercise as well as non-exercise activities. The three most essential elements for optimal physical functioning with respect to the musculoskeletal system are range of motion (flexibility), strength and aerobic capacity (endurance) (26). During the past decades, advances in research have shed light on the role of exercise as a therapy for rheumatic diseases. The most important advance is the discovery that skeletal muscle communicates with other organs by secreting proteins called myokines. Some myokines are thought to induce anti-inflammatory responses with each bout of exercise and mediate long-term exercise-induced improvements in cardiovascular risk factors, having an indirect anti-inflammatory effect (25). One of the most prominent effects of exercise is the improvement in physical capacity which is particularly beneficial for patients with RA. The decrease in visceral fat as a consequence of exercise has also indirect anti-inflammatory effects (25). In

RA it is found that the positive benefits of physical activity are a reduction of cardiovascular risk, a production of anti-inflammatory cytokines (25), an improved aerobic capacity and muscle strength, resulting in enhanced abilities in activities of daily living and health-related quality of life (27, 28). Physical activity could therefore increase RA patients' physical functioning, and probably also reduce fatigue.

**Level of physical activity**

Patients with RA are less physically active and reported more fatigue than healthy controls. But the question remains whether the level of physical activity and the level of fatigue are indeed associated in RA. If they are associated, increasing the level of physical activity could be effective to reduce fatigue in RA.

In patients with other chronic conditions such as CFS, Sjögren's syndrome, cancer and Parkinson's disease, a higher level of fatigue is associated with a lower level of physical activity (26-30). The results of this thesis showed that also in RA patients, higher fatigue levels are associated with lower levels of objectively assessed physical activity. The relation between fatigue and daily physical activity level in RA could not be explained by differences in pain, disability, coping, or cognition, or by other factors that can cause fatigue. Actigraphy, using an accelerometer, is a reliable and valid instrument for continuously and objectively measuring physical activity (31-33) and has already been used to quantify physical activity level in CFS (33), cancer survivors (34, 35), COPD (36), neuromuscular diseases (22) and in other rheumatic diseases such as osteoarthritis (37). An easier way to assess physical activity is by self-report, using questionnaires. However, for many persons it is difficult to recall their activity levels accurately, especially for light to moderate activities, and therefore the results of questionnaires may have been biased by cognitions concerning illness and disability (38). The advantage of accelerometers over self-report measures, is being able to objectively track intensity, duration and frequency of an activity even the light to moderate activities(39). Physical activity level measured in this thesis contains all kind of physical activities during a day, such as commuting, activities at work or school, household activities and leisure time activities including sport activities.

By indirect comparison, it appeared that the level of physical activity in RA patients is somewhat higher than in CFS patients (33) and lower than in disease-free breast cancer survivors (40). A comparison of physical activity level between RA patients and healthy controls measured by actigraphy is not performed yet. A disadvantage of actigraphy is that it is a rather costly and time-consuming method. Therefore, to compare the level of self reported physical activity in a large group of RA patients with the general population, the SQUASH questionnaire was used. Accordingly to this subjective measurement, RA patients reported lower

physical activity per week than the general population. Patients with RA are less active and have higher levels of fatigue than healthy controls, and this higher level of fatigue is related to a lower level of physical activity in RA. Therefore, it seems that RA patients should be encouraged to increase their physical activity level in order to decrease the level of fatigue.

**Treatment of fatigue**

Based on the results of the multidimensional model for RA fatigue, a suggestion can be made that treatments aimed at the following five factors: pain, mood disturbance, sense of control, sleep and physical functioning, could help to reduce fatigue in RA. In RA, pain is largely caused by the inflammatory process and is treated with anti-rheumatic medication (41). However, anti-inflammatory treatment alone is insufficient to treat fatigue as fatigue frequently occurs in patients with low or moderate disease activity (16). In addition a direct effect of anti-TNF on fatigue in RA has been suggested, however it appears that anti-TNF has no complementary effect on chronic fatigue (42). Finally, this thesis showed that changes in pain and fatigue occur synchronous in RA, suggesting that one does not precede the other. This may mean that the effect of pain 'causing' fatigue is limited.

Psychological interventions, notably CBT, can be used for improving sense of control over symptoms, mood and sleep quality. However, CBT can also have positive effects on physical functioning and can also be used to increase the level of physical activity, as is done in CBT for CFS for example (43, 44). In RA, studies of Hewlett and Evers indicated that CBT, alone with a psychologist or group-based, improves fatigue, coping and well-being in RA and has also positive effects on disability (45, 46). However, only moderate effects of CBT on fatigue in RA were found (45-47). A disadvantage of CBT is that trained therapists (in CBT for fatigue) are necessary and it is rather expensive. Therefore CBT interventions for fatigue are rarely offered routinely by clinical psychologists. More often RA patients with severe psychological problems are offered CBT for their problems, not for fatigue.

Little has been reported on the efficacy of CBT in reducing sleep disturbances in patients with RA (48), although occasionally improvements in subjective sleep quality after CBT has been found (49). Interestingly, a recent not yet finished trial is investigating the effect of intermittent aerobic exercise on the improvement of sleep in patients with RA (50). The hypothesis of the effect of aerobic exercise on the improvement of sleep is based on the results of cross-sectional studies that physical inactivity increases the likelihood of reporting poor sleep (51) and it has been reported that maximal aerobic capacity is lower in patients with insomnia compared to those without it (52). In addition, physical exercise interventions

have been shown to be a feasible and moderately effective non-pharmacological treatment for improving sleep in healthy and in clinical populations (53, 54). Besides a positive effect on sleep, increasing physical activity level could increase RA patients' physical functioning. A systematic review showed a significant improvement in physical functioning by graded exercise therapy (GET) in CFS patients: exercise in which the incremental increase in exercise was mutually set (44). While acknowledging that CFS and RA are different disorders, increasing physical activity could also be a promising treatment for RA fatigue.

**Increasing physical activity level as a treatment for fatigue**

Physical activity in the broadest context includes all body movements resulting in energy expenditure, including sports as well as non-sports activities such as occupational and household activities (55). Sports or exercise is a subset of physical activity, which can be defined as planned, structured and repetitive activity with the objective of improving or maintaining physical fitness (55).

Consequently, increasing physical activity level can be performed with or without inclusion of intensive exercising. However, physical activity below a minimum intensity will not challenge the body sufficiently to result in increased aerobic capacity and improvements in other physiological parameters (56). To increase physical functioning in RA patients by increasing strength and aerobic capacity, dynamic exercise seems effective. A cardiorespiratory (dynamic) aerobic exercise should be performed at 50%-80% of the maximal heart rate (220-age) to increase aerobic capacity (57).

Systematic reviews concluded that dynamic exercise in patients with RA is effective with respect to the improvement of aerobic capacity and muscle strength, without detrimental effects on disease activity, pain or radiological joint damage (58, 59) and more benefits were seen in these parameters with high intensity exercise, compared to low intensity exercise (60). Regarding fatigue, there is some evidence to suggest that several exercises provide benefit in RA (61, 62). These meta-analyses included different forms of physical activity (pool-based therapy, yoga, dynamic strength training, stationary cycling, low impact aerobics and Tai Chi) with different intensities. However, only one single RCT in patients with RA has been performed on aerobic exercise, with an intensity between 50%-80% of the maximal heart rate, with fatigue as dedicated primary outcome measure (63). This RCT found that fatigue decreased significantly for the exercise group compared to the control group (63). However, there are some other trials performing an aerobic exercise program in RA and did measure fatigue as outcome but did not publish the results of fatigue. Therefore, in this thesis a meta-analysis was performed to summarize the limited evidence of the effect of an aerobic exercise program on fatigue and to get a better estimate of the mean effect.

Published and notably also unpublished fatigue data were collected from trials. The results of this meta-analysis showed that a supervised aerobic land-based exercise program may be beneficial to treat fatigue in RA at 12 or 24 weeks, although the effect for both time points was small and only significant at 12 weeks. It seems that maintenance is a concern; patients stopped exercising or exercised less intensive after the supervised part of the training program. To maintain exercising patients should be motivated and coached.

Exercise seems a promising intervention to treat fatigue in RA, although there is no definitive evidence for its efficacy. In other chronic diseases such as breast cancer survivors, a supervised aerobic exercise program is effective for fatigue (64). However, in the context of CBT for CFS and post-cancer fatigue patients, it appeared that an increase in physical activity level was not the mediator of a reduction in fatigue level (34, 35, 65). It turned out that cognitions mediated the decrease in fatigue and not the increase in physical activity. However this does not mean that increasing physical activity level could not be effective in reducing fatigue in RA, apart from the question of mediative factors. Future research is necessary to investigate the effects of increasing physical activity by an exercise program on fatigue in RA, and next also the mediators of these effects.

**Effect of exercise on fatigue in patients with rheumatoid arthritis: A pilot study**

A pilot study was performed by our group with the aim to investigate the feasibility of 12-weeks of supervised aerobic exercise, versus no exercise, on fatigue levels in 24 patients with RA having severe fatigue for at least 6 months. For this pilot study we could make use of a training facility at noon, 2-3 times a week. However, the combination of training frequency and time point appeared to be a hindrance for many potential participants and it was not possible to include enough patients in 6 months. Finally, five patients were included in the intervention group and two patients in the control group. The intervention consisted of a 12-week supervised aerobic exercise program on a bicycle ergometer. The first 6 weeks RA patients performed 2 times a supervised personalized interval training of approximately 50 minutes and 3 times per week in the second period of 6 weeks. The control group did not participate in the supervised aerobic exercise program. Measurements of fatigue, aerobic performance (VO2 max), disease activity (DAS28), pain (VAS), disability (HAQ), self-efficacy concerning fatigue, coping, grip strength, cardiovascular risk factors, kinesiophobia, daily activities and sport participation were measured at four time points, both in the intervention group and in the control group. The pilot study was not aimed at finding a treatment effect, but to gain insight in the feasibility and limitations of an exercise program for RA patients. The participating RA patients were very enthusiastic and content with the exercise program, felt less fatigued and felt encouraged

to continue exercising. The patients experienced that that there was need for a more varied program, than cycling alone. A joined warming up with various types of exercises would be a nice addition to the program. RA patients mentioned they would like to train their whole body instead of only their legs, with additive types of sport; this type of combined exercise may feel more balanced.

Therefore in future studies, it would be beneficial if patients would choose their preferred exercise mode themselves, self-determine when to exercise, self-pace their exercise and have monitoring and feedback. A personalized graded activity program combines the operant-conditioning behavioural approach with increasing the activity level, as applied in osteoarthritis and the chronic fatigue syndrome (66-68) and fits well to these needs. The program is directed at enhancing physical activity adherence and gradually increasing the amount of physical activity in a time-contingent way so that activities are gradually increased by preset quotas regardless of impairments (69). To facilitate initiation and adherence patient perceptions about fatigue and physical activity will be explored and discussed with the patient by means of motivational interviewing techniques. For the maintenance phase of physical activity, RA patients should self-pace their exercise and have monitoring and feedback besides being coached by a supportive professional. Monitoring and feedback could be performed by an internet-based individualized training even in combination with group contact moments together with other RA patients (70, 71). Other forms of internet-based supervised monitoring and motivation of physical activity level are mobile applications for advice regarding physical activity exercises developed in patient groups such as Bechterew disease (72) and in Parkinson's disease (73).

**Clinical implications and future research**

There still is no evidence based strategy available which is sufficiently effective for treatment of fatigue in RA patients. In the clinic, for RA patients pain and fatigue are the most important symptoms of the disease. While disease activity can be well treated nowadays, there is still not enough treatment possibilities to treat fatigue. The studies in this thesis provide knowledge about which factors the treatment of fatigue in RA patients should be focused on: sleep quality, physical functioning, pain, sense of control and mood disturbance.

This has several clinical implications for the treatment of RA fatigue:

- In RA, pain and fatigue should both be treated.
- Sleep quality is another issue that should be paid attention to in the clinic.
- A psychological intervention, preferably CBT, could be an effective treatment for the factors mood disturbance, sense of control, sleep functioning and

eventually physical functioning.

- Increasing physical activity level could be a promising treatment for RA fatigue, by breaking a vicious circle: a higher level of physical activity is associated with a lower level of fatigue which may lead to less mood disturbance and more sense of control over fatigue, associated with more physical activity in RA.
- Increasing physical activity level can be performed with an exercise program and/or with a graded activity program.

However, the optimal and most effective way to increase physical activity level in RA is not known yet and we don't know the effectiveness of such an intervention on fatigue. One of the big issues is that patients have difficulties to adhere and comply to prolonged exercise and to maintain activity level in daily life. Patient perceived barriers and limitations of exercise that should be dealt with in devising and performing interventions. Accordingly future research should be performed:

- To investigate if a personalized graded activity program is effective to increase the level of physical activity in RA patients.
- It should be investigated how to maintain physical activity e.g. by monitoring and feedback and the best way to incorporate physical activity in RA patients' daily life.
- To provide evidence whether an aerobic exercise program is effective for fatigue in RA patients, especially in severe fatigue.
- The most beneficial intensity of aerobic exercise, irrespective of the mode of exercise (e.g. cycling, swimming, walking), to treat RA fatigue should be investigated.
- To investigate the mediators of the effect of increasing physical activity on fatigue in RA.

If future research confirms that exercise indeed is effective and if the most beneficial intensity of aerobic exercise to treat fatigue would be known, physical exercise can be implemented and finally clinicians could provide this guidance to patients. However, apart from a possible effective treatment for fatigue in RA, physical activity has several other beneficial effects on health for people with RA, such as reduction of cardiovascular risk, increasing aerobic capacity, increasing muscle strength, and reducing pain and disability.

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# Chapter 8

## Summary

In RA, fatigue is a frequently occurring and patient-relevant complaint which by patients is experienced as debilitating and restricting daily functioning. At least 40% of the RA patients is severely fatigued and until now no established treatment for fatigue in RA is available. This thesis was performed with the aim to gain more insight into factors associated with fatigue in RA, and especially the association between physical activity and fatigue. We hypothesized that RA patients with severe fatigue may come into a vicious circle: a decrease in physical activity is associated with a higher level of fatigue, which leads to more mood disturbance and less sense of control over fatigue, associated with a further decrease in physical activity, etcetera. Clarifying the relationships between fatigue, physical activity and other factors may lead to better understanding of fatigue and improvement of treatment of fatigue. These ideas are delineated in **chapter 1**.

Pain and fatigue are mentioned by RA patients as the two most disturbing symptoms of the disease and usually they do co-occur. From a cause-effect point of view, it is not clear whether a change in pain may precede a change in fatigue, or the other way round? In **chapter 2** the course of fatigue and the course of pain in RA patients over a period of one year was investigated while pain and fatigue were measured every month. It was shown that, on average, the course of pain and fatigue were stable over time, but within patients there was considerable monthly fluctuation in pain and fatigue scores. However, a change in fatigue is positively associated with a change in pain at the same time. Thus, a synchronous relation between fatigue and pain was found rather than showing a temporal relationship with a time lag. Probably both pain and fatigue are driven by common factors, that may probably be psychologically of nature. The clinical implication is that both manifestations should be treated because it cannot be expected that an improvement in one is followed by an improvement in the other.

In patients with chronic disorders other than RA, such as the Chronic Fatigue Syndrome (CFS), fatigue seems to be associated with a low level of physical activity. However, whether such an association also exists in RA has not been reported so far. In **chapter 3** it was investigated whether objectively measured activity levels and activity patterns were associated with fatigue levels in patients with RA, and whether pain, disability, coping, and/or cognition are associated with—or influence—the level of activity among patients with RA. Physical activity in RA has not been measured objectively before, but we measured the level of physical activity using an actometer during 14 consecutive days. This study showed that the average activity level of patients with RA appears to be lower than in healthy controls and higher than in patients with CFS. Moreover, patients with RA who had a high level of daily physical activity were less fatigued than patients with low daily physical activity; and, the level of activity was not associated with pain, disability, coping, or cognition.

While fatigue is prevalent in RA, it appears not to be uncommon in the general population. To investigate whether fatigue indeed is more severe in RA than in the general population, in **chapter 4** the level of fatigue between RA patients and the general Dutch population was compared. In addition, the level of physical activity (subjectively measured) was compared between RA patients and the general population and it was described how many RA patients were engaged in sports and in which sport activities. Interestingly, both half of the RA patients (52%) and half of the people from the general population (54%) were meeting the physical activity recommendation. At the same time it showed that patients with RA do have less minutes of physical activity per week and higher levels of fatigue, compared to the general population. At least once a week, 59% of the RA patients participated in sports, with fitness, swimming, strength training and walking as the most popular sports. Most frequently mentioned limitations to begin with a new sport are physical impairment, unawareness of the options and fear of injuries.

Besides pain and less physical functioning, previous studies reported that depressive symptoms, sleep disturbances, and psychological factors such as self-efficacy and coping strategies are related to fatigue severity in RA. How these factors together may contribute to fatigue in RA is studied in a multidimensional model for fatigue developed and tested in **chapter 5**. According to the multidimensional path analysis model developed in this study, RA fatigue was influenced directly by poor sleep quality and physical functioning, and indirectly by sense of control, mood and pain. This indicates 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. Less sense of control was associated with more mood disturbance, more pain and less physical functioning. The five factors: pain, mood disturbance, sense of control, sleep disturbances and less physical functioning, found in this model can be regarded as important associated factors of fatigue in RA with possible implications for fatigue treatment. If these factors could effectively be treated, this may lead to improvement in patients' fatigue.

There is still limited evidence regarding effective interventions to treat RA fatigue. In CFS there is most evidence for beneficial effects of cognitive behavioural therapy and for exercise. It therefore is useful to regard these as candidate interventions in RA, while recognizing different mechanisms may be involved in fatigue in RA and in CFS. In RA, only a moderate effect of cognitive behavioral therapy for fatigue is found. As an increased level of physical activity is associated with a lower level of fatigue in RA, increasing the level of physical activity could be a reasonable treatment indeed. Presumably, training the aerobic ca-

pacity of an individual, by exercising between 50-90% of maximal heart rate, has positive effects on overall condition/physical fitness and could therefore also have positive effects on fatigue in patients with RA. However, there is a lack of evidence regarding training aerobic capacity and the effect on RA fatigue. A meta-analysis of aerobic exercise programs on fatigue was performed in **chapter 6**, including published as well as unpublished fatigue outcomes. The results of this meta-analysis showed that a supervised aerobic exercise training may be beneficial to treat fatigue in RA, especially on the short-term, but the effects sizes were small.

In **chapter 7**, the main findings were discussed and the clinical implications and recommendations for future research were given. The results of this thesis showed that patients with RA are less active and have higher levels of fatigue than healthy controls, and this higher level of fatigue is related to a lower level of physical activity in RA. Raising daily physical activity level, with or without intensive exercising, could be a promising treatment for fatigue in RA by breaking a vicious circle. Future research should be performed to confirm this. If exercise indeed is effective, this would constitute a relatively cheap intervention which can be implemented in a guideline for the inter-disciplinary treatment of fatigue in RA and implemented through patient organizations.

8

# Chapter 9

## Nederlandse samenvatting

Vermoeidheid wordt door veel patiënten met Reumatoïde Artritis (RA) als klacht aangegeven. Tenminste 40% van de patiënten met RA heeft last van ernstige vermoeidheid, met grote gevolgen voor de kwaliteit van leven van deze patiënten. Er is tot op heden nog geen algemeen geaccepteerde effectieve behandeling gevonden voor vermoeidheid bij RA.

In dit proefschrift getiteld: ***Physical activity and fatigue in rheumatoid arthritis: a vicious circle?*** is onderzocht welke factoren een relatie hebben met vermoeidheid bij patiënten met RA. Speciaal wordt gekeken naar het verband tussen lichamelijke activiteit en vermoeidheid. Onze hypothese was dat patiënten met RA met vermoeidheid in een vicieuze cirkel raken: een verminderde lichamelijke activiteit leidt tot een toename in vermoeidheid, deze toename in vermoeidheid leidt tot het idee minder vat te hebben op deze vermoeidheid, wat weer leidt tot nog minder lichamelijke activiteit, enzovoort. Het doorbreken van deze vicieuze cirkel zou een verbetering kunnen geven van de vermoeidheid. Het doel van dit proefschrift was enerzijds om inzicht te krijgen in de relatie tussen lichamelijke activiteit en vermoeidheid en anderzijds het in kaart brengen van andere belangrijke factoren die een verband hebben met vermoeidheid bij patiënten met RA. Dit zou kunnen leiden tot een betere behandeling van vermoeidheid bij RA.

In **hoofdstuk 1** van dit proefschrift wordt een inleiding gegeven over vermoeidheid bij RA. Pijn en vermoeidheid zijn beide heel belangrijke klachten voor patiënten met RA en deze twee klachten komen vaak tegelijkertijd voor. Het is echter niet bekend of pijn veroorzaakt wordt door vermoeidheid of dat vermoeidheid juist veroorzaakt wordt door pijn; of is er eerder een gezamenlijke oorzaak? In **hoofdstuk 2** is de relatie tussen vermoeidheid en pijn in een longitudinale studie onderzocht. Een groep patiënten met RA heeft een jaar lang de mate van vermoeidheid en de mate van pijn bijgehouden. Op die manier konden we kijken of toename of afname in pijn gevolgd werd, of vooraf ging, aan veranderingen in vermoeidheid. De resultaten van deze studie laten zien dat gemiddeld genomen, pijn en vermoeidheid helemaal niet veel veranderen. Maar bij individuele patiënten zijn er wel schommelingen in pijn en vermoeidheid. Het bleek dat een toename (of afname) van pijn samen ging met een gelijktijdige toename (of afname) van vermoeidheid; het een ging dus niet aan het ander vooraf. Het lijkt er daarom op dat vermoeidheid en pijn bij RA aparte klachten zijn en daarom ook allebei behandeld moeten worden.

Onze hypothese was dat bij patiënten met RA met vermoeidheid een verminderde lichamelijke activiteit leidt tot een toename in vermoeidheid. Deze toename in vermoeidheid leidt tot het idee minder vat te hebben op deze vermoeidheid, wat weer leidt tot nog minder lichamelijke activiteit. In **hoofdstuk 3** van dit proefschrift is daarom onderzocht of vermoeidheid en lichamelijke activiteit aan elkaar gerelateerd zijn. Het zou kunnen dat patiënten met RA die meer moe

zijn ook minder bewegen. Daarnaast werd gekeken of de hoeveelheid dagelijkse beweging samenhangt met pijn, verminderd lichamelijk functioneren, omgang met RA klachten (coping strategieën) en opvattingen over RA klachten (cognities). Daartoe is gedurende 14 achtereenvolgende dagen de dagelijkse activiteit bij patiënten met RA objectief gemeten met behulp van een apparaatje gedragen om de enkel, een actometer. Volgens de resultaten was er een verband: meer dagelijkse lichamelijke beweging hing samen met minder vermoeidheid. De hoeveelheid dagelijkse beweging hing echter niet samen met pijn, lichamelijk functioneren, de manier van omgaan met de klachten en de manier van denken over de klachten.

Om inzicht te krijgen hoeveel patiënten met RA nu eigenlijk bewegen en hoe moe ze zijn in vergelijking tot gezonde mensen, hebben we de hoeveelheid dagelijkse beweging en de mate van vermoeidheid bij patiënten met RA in **hoofdstuk 4** vergeleken met een grote groep mensen uit de algemene Nederlandse bevolking. Dagelijkse activiteit werd gemeten met behulp van een vragenlijst over bewegen. In deze vragenlijst werd bij patiënten met RA ook nagevraagd hoe vaak ze deelnemen aan sportactiviteiten en welke sport zij beoefenen en de eventuele beperkingen om niet aan sport deel te nemen beschreven. De resultaten uit deze vragenlijst lieten zien dat patiënten met RA een gemiddeld hogere mate van vermoeidheid hebben en minder minuten per week besteden aan dagelijkse lichamelijke activiteiten in vergelijking met de algemene Nederlandse bevolking. Echter, er wordt geen verschil gevonden in het percentage patiënten met RA dat voldoet aan de norm van ≥5 keer per week een middelmatig intensieve inspanning van ≥ 30 minuten, vergeleken met het percentage uit de algemene Nederlandse bevolking wat voldoet aan deze norm, voor beide groepen was dit ongeveer 50%. Van de patiënten met RA neemt 59% ten minste 1 keer per week deel aan een sport en daarbij zijn de meest populaire sporten onder patiënten met RA fitness, zwemmen, krachttraining en wandelen. Daarnaast heeft 32% van de patiënten met RA zin om aan een nieuwe sport te beginnen. Patiënten met RA geven als redenen om niet te sporten aan dat het lichamelijk niet mogelijk is, dat zij niet op de hoogte zijn van het bestaan van sportmogelijkheden of dat zij bang zijn voor blessures.

Naast lichamelijke activiteit spelen ook andere factoren een rol bij vermoeidheid bij RA. Resultaten uit verschillende studies laten zien dat de factoren pijn, verminderd lichamelijk functioneren, depressieve symptomen, slaapklachten, en psychologische factoren zoals een negatieve self-efficacy (het idee geen vat te hebben op de klachten) en de manier van omgaan (coping strategieën) een relatie hebben met een hogere mate van vermoeidheid bij RA. Echter, deze mogelijke voorspellers voor vermoeidheid geven nog geen informatie over een oorzakelijk verband en het is nog niet bekend hoe deze factoren gezamenlijk bijdragen aan

vermoeidheid. In **hoofdstuk 5** van dit proefschrift is daarom een multi-dimensioneel model voor vermoeidheid getoetst om te onderzoeken hoe deze factoren samen bijdragen aan vermoeidheid. Door middel van een statistische techniek zijn directe en niet directe verbanden tussen de variabelen getoetst op basis van onze hypothese. Uit de resultaten van dit model blijken slechte slaapkwaliteit en verminderd lichamelijk functioneren direct gerelateerd te zijn aan meer vermoeidheid bij RA. Deze vijf factoren: pijn, angst en depressie, geringere self-efficacy, slechter slapen en slechter lichamelijk functioneren lijken het sterkst verbonden te zijn met vermoeidheid bij RA . Als deze factoren effectief behandeld worden, zal dit kunnen leiden tot een afname van vermoeidheid bij de patiënt met RA.

Er is momenteel geen effectieve behandeling voor vermoeidheid bij RA. Er is wel wat bewijs dat cognitieve gedragstherapie, wat een effectieve behandeling is bij patiënten met het chronisch vermoeidheidssyndroom, ook zou kunnen helpen bij verlichting van vermoeidheid bij patiënten met RA. Echter, de effecten van cognitieve gedragstherapie op vermoeidheid bij RA zijn beperkt. Eerder beschreven we een relatie tussen meer dagelijkse lichamelijke activiteit en minder vermoeidheid bij patiënten met RA. Meer dagelijkse activiteit zou daarom een goede aanvullende en ondersteunende effectieve behandelingsmogelijkheid kunnen zijn voor vermoeidheid bij patiënten met RA. Deze behandeling zou de vicieuze cirkel kunnen doorbreken: meer lichamelijke activiteit zou bij patiënten met RA met vermoeidheid tot een vermindering in vermoeidheid kunnen leiden, deze vermindering in vermoeidheid leidt tot het idee meer vat te hebben op deze vermoeidheid, wat weer zou kunnen leiden tot nog meer lichamelijke activiteit.

Naast meer dagelijkse activiteit in het algemeen, is het mogelijk dat sporten een nog groter effect kan hebben op vermoeidheid. Daarom hebben we in **hoofdstuk 6** van dit proefschrift een meta-analyse uitgevoerd naar het effect van sporten op vermoeidheid. In deze meta-analyse werden alle gerandomiseerde gecontroleerde studies geïncludeerd die een inspanningsprogramma onder begeleiding van een deskundige bij patiënten met RA hebben uitgevoerd. Zowel studies die vermoeidheid als uitkomstmaat hebben gerapporteerd alsmede de studies die dat niet hebben gedaan zijn opgenomen in onze meta-analyse. De resultaten van deze meta-analyse laten zien dat een inspanningsprogramma gericht op verbetering van de fitheid ook positieve effecten kan hebben op vermoeidheid, maar de gevonden effecten zijn klein.

In **hoofdstuk 7** worden de belangrijkste bevindingen bediscussieerd. Klinische implicaties en aanbevelingen voor toekomstig onderzoek worden gegeven. De resultaten van dit proefschrift laten zien dat patiënten met RA minder lichamelijk actief en meer vermoeid zijn dan mensen zonder deze ziekte. Bij patiënten met RA hangt meer vermoeidheid samen met minder lichamelijke activiteit. Door middel van meer lichamelijke activiteit in het algemeen, en/of het volgen van

een inspanningsprogramma kan de vicieuze cirkel doorbroken worden. Hiermee kan het een veelbelovende behandeling zijn voor vermoeidheid bij RA.

Nieuw onderzoek zal moeten worden uitgevoerd, specifiek bij ernstige vermoeide patiënten met RA, om dit bewijs te kunnen leveren en daarnaast moet onderzocht worden hoe deze behandeling het beste in het dagelijkse leven van de patiënt ingepast kan worden. Mocht een lichamelijk inspanningsprogramma voldoende effectief blijken om vermoeidheid te verminderen, dan zou dit deel kunnen uitmaken van een richtlijn voor de behandeling van vermoeidheid bij RA.

# List of abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| BDIPC | Beck Depression Inventory for primary care |
| BMI | Body Mass Index |
| BRAF MDQ | Bristol Rheumatoid Arthritis Fatigue Multi-dimensional Questionnaire |
| CAL | Causal Attribution List |
| CBT | Cognitive Behavioural Therapy |
| CFI | Comparative Fit Index |
| CFS | Chronic Fatigue Syndrome |
| CIS | Checklist Individual Strength |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRP | C-Reactive Protein |
| DAS28 | Disease Activity Score in 28 joints |
| DI | Disability Index |
| DMARD | Disease Modifying Antirheumatic Drug |
| ESR | Erythrocyte Sedimentation Rate |
| FACIT-F | Functional Assessment Chronic Illness Therapy Fatigue |
| FCS | Fatigue Catastrophizing Scale |
| FM | Fibromyalgia |
| FSS | Fatigue Severity Scale |
| GET | Graded Exercise Therapy |
| GH | General Health |
| HAQ | Health Assessment Questionnaire |
| IQR | Interquartile Range |
| MAF | Multidimensional Assessment of Fatigue |
| MPCI-F | Modified Pain Coping Inventory for Fatigue |
| MS | Multiple Sclerosis |
| MTX | Methotrexate |
| NBS | Nijmegen Biomedical Study |
| NRS | Numerical Rating Scale |
| OMERACT | Outcome Measures in Rheumatology Clinical Trials |
| RA | Rheumatoid Arthritis |
| RCT | Randomized Controlled Trial |
| RMSEA | Root Mean Square Error of Approximation |
| RSO | Richtlijnen Sportdeelname Onderzoek |
| SCL-90 | Symptom Checklist-90 |
| SD | Standard Deviation |
| SE | Standard Error |
| SEM | Structural Equation Modeling |
| SES | Self-Efficacy Scale |

| | |
|---|---|
| SF-36 | Short Form health survey 36-item |
| SFQ | Shortened Fatigue Questionnaire |
| SJC28 | Swollen Joint Count in 28 joints |
| SMD | Standardized Mean Difference |
| SQUASH | Short QUestionnaire to Assess Health |
| SRMR | Standardized Root Mean Residual |
| TJC28 | Tender Joint Count in 28 joints |
| VAS | Visual Analog Scale |

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Sanne, juli 2015

# Over de auteur

Op 15 augustus 1986 is Sanne Annemarie Adriane van Dartel geboren te ’s-Hertogenbosch. Sanne is opgegroeid in het Brabantse Schijndel als jongste in een gezin met 3 kinderen. In 1998 ging ze naar Gymnasium Beekvliet, te Sint-Michielsgestel. Tijdens haar jeugd is Sanne actief schaatster geweest en heeft ze in verschillende gewestelijke selecties en baanselecties geschaatst. In 2004 is ze geslaagd voor het gymnasium met de profielvakken natuur en gezondheid. In datzelfde jaar begon ze aan de opleiding biomedische wetenschappen aan de Katholieke Universiteit Nijmegen (nu Radboudumc Nijmegen). In het kader van haar hoofdvak bewegingswetenschappen heeft ze twee stages gelopen. Een eerste stage heeft ze gelopen bij de afdeling bewegingswetenschappen aan de Vrije Universiteit te Amsterdam onder supervisie van Dr. A. Daffertshofer en Dr. J.J. de Koning. Tijdens deze stage heeft ze onderzoek gedaan naar de biomechanische en fysiologische factoren tijdens de overgang van zittend naar staand en van staand naar zittend fietsen op een stijgende en dalende helling. Haar tweede stage heeft ze gelopen bij de afdeling Fysiologie van het Radboudumc onder supervisie van Dr. T. Eijsvogels en Prof. Dr. M.T.E. Hopman. Tijdens deze stage heeft ze een omvangrijk onderzoek uitgevoerd naar de thermofysiologische belasting, elektrolyten- en vochtbalans bij 250 hardlopers die deelnamen aan de 7-heuvelenloop. In september 2009 behaalde Sanne haar Master of Science diploma. Na haar afstuderen heeft ze gewerkt als junior onderzoeker op de polikliniek orthopedie van het Radboudumc waarbij ze verantwoordelijk was voor de dataverzameling van het Klinisch Score Station. In september 2010 is ze als onderzoeker in opleiding begonnen binnen de afdeling reumatische ziekten van het Radboudumc. Het eerste jaar van haar promotieonderzoek heeft ze onderzoek gedaan bij patiënten met reumatoïde artritis naar het risico op ernstige infecties bij het gebruik van TNF blokkers. Tijdens de rest van haar opleidingstraject heeft ze onderzoek gedaan naar inspanning en vermoeidheid bij patiënten met reumatoïde artritis, waaruit dit proefschrift tot stand is gekomen. Haar promotieonderzoek werd begeleid door Prof. Dr. P.L.C.M. van Riel, Dr. J. Fransen, Dr. J.W.J. Repping-Wuts en Prof. Dr. G. Bleijenberg. Per half mei 2015 is Sanne werkzaam als coördinator zorginnovatie op de afdeling reumatologie in het Bernhoven ziekenhuis te Uden. Sanne is getrouwd met Jan Rongen en samen hebben zij een dochter (Floor).

# List of publications & RIHS PhD portfolio

**van Dartel SA**, Fransen J, Kievit W, Flendrie M, den Broeder AA, Visser H, et al. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry.
Annals of the Rheumatic Diseases. 2013;72(6):895-900.

**van Dartel SA**, Fransen J, Kievit W, Dutmer EA, Brus HL, Houtman NM, et al. Predictors for the 5-year risk of serious infections in patients with rheumatoid arthritis treated with anti-tumour necrosis factor therapy: a cohort study in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry.
Rheumatology (Oxford). 2013;52(6):1052-7.

**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 & Research (Hoboken). 2013;65(6):862-9.

**Rongen-van Dartel SA**, Repping-Wuts H, van Hoogmoed D, Knoop H, Bleijenberg G, van Riel PL, et al. Relationship between objectively assessed physical activity and fatigue in patients with rheumatoid arthritis: inverse correlation of activity and fatigue.
Arthritis Care & Research (Hoboken). 2014;66(6):852-60.

**Rongen-van Dartel SA**, Repping-Wuts H, Flendrie M, Bleijenberg G, Metsios GS, van den Hout WB, et al. The effect of aerobic exercise training on fatigue in rheumatoid arthritis: a meta-analysis.
Arthritis Care & Research (Hoboken). 2015. Epub 2015/01/28.

**Rongen-van Dartel SA**, Repping-Wuts H, Donders R, van Hoogmoed D, Knoop H, Bleijenberg G, et al. A multidimensional 'path analysis' model of factors explaining fatigue in rheumatoid arthritis.
Clinical and Experimental Rheumatology 2015.

# RIHS PhD portfolio

Institute for Health Sciences
Radboudumc

| Name PhD student: Sanne Rongen-van Dartel<br>Department: Rheumatology<br>Graduate School: Radboud Institute for Health Science | PhD period: 01-09-2010 – 23-04-2015<br>Promotor(s): Prof. dr. P.L.C.M. van Riel & Prof. dr. G. Blijenberg<br>Co-promotor(s): dr. J. Fransen & dr. J.W.J. Repping-Wuts | |
|---|---|---|
| | year | ECTS |
| **Training activities** | | |
| a) courses and work-shops: | | |
| - Management for Phd students, Radboud University Nijmegen | 2011 | 3 |
| - Academic writing, Radboud University Nijmegen | 2012 | 3 |
| - Advanced analysis of prognosis studies, erasmus winter programme, Rotterdam | 2012 | 3 |
| - RIHS introduction course for Phd students, Radboud University Nijmegen | 2012 | 1.4 |
| - Presenteren eigen onderzoek, Radboud University Nijmegen | 2012 | 1.5 |
| - Clinimetrics: assessing measurement properties of health measurement, VU Amsterdam | 2013 | 3 |
| - Begeleiden van onderzoeksstages, Radboud University Nijmegen | 2013 | 0.6 |
| - Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK), Radboud University Nijmegen | 2013 | 1.4 |
| - cursus solliciteren en netwerken, Radboud University Nijmegen | 2014 | 0.6 |
| b) Symposia & congresses: | | |
| the EUropean Leage Against Rheumatism congress (poster presentation) | 2011 | 0.6 |
| Nederlandse Vereniging Reumatologie Papendal (oral presentation) | 2011 | 0.6 |
| Nederlandse Vereniging Reumatologie Papendal (poster presentation) | 2012 | 0.6 |
| the EUropean Leage Against Rheumatism congress (poster presentation) | 2013 | 0.6 |

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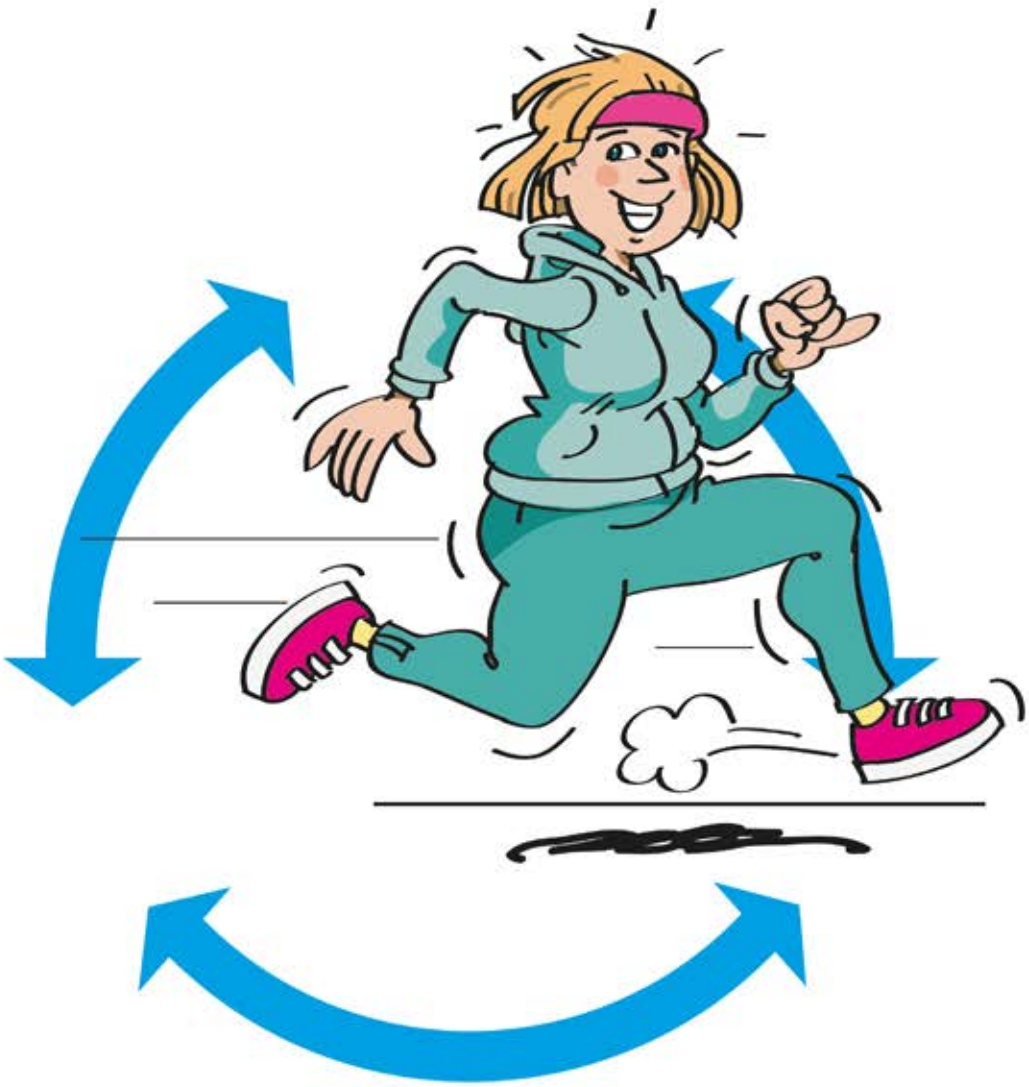
|---|---|---|
| c) other: | | |
| Seminars and colloquia at the Department of rheumatology, Radboudumc, Nijmegen | 2010-2014 | 3.6 |
| Review scientific publication | 2011-2015 | 0.4 |
| **Teaching activities** | | |
| d) supervision of internships: | 2012-2013-2014 | 4 |
| Total | | 23.9 |



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