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ORIGINAL REPORT

LOW AEROBIC CAPACITY AND PHYSICAL ACTIVITY NOT ASSOCIATED WITH FATIGUE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A CROSS-SECTIONAL STUDY

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Objective: **To explore whether low aerobic capacity and physical activity are associated with fatigue, when controlling for age, gender, pain and depressive symptoms in persons with rheumatoid arthritis.**

Methods: **In 60 individuals fatigue (Multidimensional Assessment of Fatigue scale; MAF), disease activity (Disease Activity Score-28; DAS28), pain, physical and psychological status (Arthritis Impact Measurement Scales 2; AIMS2), depression (Hospital Anxiety and Depression Scale; HADS), aerobic capacity and physical activity (Short Questionnaire to Assess Health-enhancing physical activity; SQUASH) were measured. Regression analysis was performed to study the variance of fatigue explained by aerobic capacity and physical activity.**

Results: **Mean (standard deviation (SD)) age of participants was 51.8 (SD 10.4) years and 73.3% were women. Duration of disease was 10.2 (SD 0–41) years and mean disease activity score was 3.4 (SD 1.4).**

Mean Global Fatigue Index was 20.3 (SD 10.5). Physical function was 1.6 (SD 1.1) and psychological status 3.1 (SD 0–8) on the AIMS2. Pain score was 4.1 (SD 2.0) and median depression score was 3.2 (range 0–15). Total amount of physical activity was 176.9 (10.6–1,492.3) METhours/week and VO_2max was 27.8 (SD 3.8) ml/kg/min. Backward multiple regression showed a statistically significant relationship with depressive symptoms only ($t = 5.4$, $p < 0.001$), which explained 33% of variance of fatigue in patients with RA.

Conclusion: **Depression, but not aerobic capacity or physical activity, contributed to fatigue. However, no relationship was found between aerobic capacity and fatigue.**

Key words: arthritis; rheumatoid; physical activity; aerobic capacity; fatigue; depression.

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INTRODUCTION

Rheumatoid arthritis (RA), a chronic inflammatory disease characterized by polyarthritis and erosive synovitis, is associated with progressive impairments and activity limitations (1, 2). The prevalence of RA in the Dutch adult population is approximately 1%, and women have a 3-fold higher risk of developing RA (3).

Although most of the symptoms of RA are located in the joints, RA also produces general symptoms, such as fatigue (4). A consensus definition for fatigue has not yet been formulated in the current literature. Often fatigue is defined as the enduring, subjective sensation of generalized tiredness or exhaustion and a decreased capacity for physical and mental work (4). In RA-related research fatigue is described as a multicausal, multidimensional and complex concept in which psychological, biochemical and physiological mechanisms play a role (4–6). Depending on the definition it is estimated that 42–93% of individuals with RA experience fatigue (7). Individuals with RA experience more frequent, as well as higher levels of, fatigue compared with the general population (3), but disease activity does not appear to be the major predictor of fatigue (7–10).

Several studies show a positive effect of exercise programmes on fatigue (10–12). It is unclear whether this positive effect is the result of increased aerobic capacity through exercise or of improved mood and psychosocial well-being (7, 11, 13) and positive changes in depressive symptoms (14), or both.

One theory is that patients with RA experience a vicious cycle of fatigue leading to inactivity, leading to deconditioning, leading to fatigue. It is suggested that experiencing fatigue may have a negative impact on physical activity (PA) and exercise because there is less energy to expend (4). Reduced frequency, duration and intensity of PA is associated with deconditioning; loss of physical fitness, including loss of aerobic capacity. Decreased aerobic capacity may lead to higher levels of exertion when conducting activities of daily living (15), resulting in (premature) fatigue. Although it is generally assumed that PA and aerobic capacity are decreased

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in patients with RA, there is little evidence available to support this assumption (1).

Information on patients' actual level of PA is incomplete and the results of studies are not comparable, due to differences in the assessment of PA (1). The few studies that compared aerobic capacity of patients with early (16) and late (16–19) RA and healthy controls detected no differences in aerobic capacity. Both patients and controls, however, had decreased aerobic capacity compared with normative values. This may reflect the fact that half the general population is inactive (20, 21). It remains unclear whether inactivity and decreased aerobic capacity are correlated with higher levels of fatigue experienced by patients with RA compared with healthy controls.

Of patients with RA, 15–23% also experience depressive symptoms (22), which correlate with pain and work status. Symptoms related to depression may express themselves as arthritis-related symptoms, such as fatigue, difficulty in performing everyday activities and inactivity. Authors agree on pain and depression being important predictors of fatigue in patients with RA (3, 7, 13, 23–26). Persons with RA rate fatigue as an important symptom interfering with their quality of life (27). In order to develop RA-specific interventions to enhance quality of life, it is important to understand the specific contribution of factors related to fatigue.

We hypothesized that low aerobic capacity capacity and PA are associated with fatigue, when controlling for age, gender, pain and depressive symptoms in persons with RA.

PATIENTS AND METHODS

Study population

Potential participants were identified at the rheumatology department at Martini Hospital in Groningen, The Netherlands, by reviewing office charts. Participants were eligible if they had a rheumatologist-confirmed diagnosis of RA according to the 1987 American College of Rheumatology criteria (28) and were 18–65 years of age. Participants were excluded if they had other rheumatic diseases, a history of lower extremity joint replacement, cardiovascular disease or high cardiovascular risk according to the "Guidelines for Exercise Testing and Prescription" of the American College of Sports Medicine (ACSM) (29).

Recruitment of participants

Potential participants were invited by the rheumatologist to participate in the study when they came for regular office visits. When subjects agreed to participate after reading information on the study, they were screened by a trained rheumatology nurse. Participants with cardiovascular or metabolic disease risk factors and major symptoms according to the "Guidelines for Exercise Testing and Prescription" of the ACSM (29) were excluded by the nurse. The recruitment process is illustrated in Fig. 1.

After signing an informed consent participants were asked to complete questionnaires. All questionnaires used were validated Dutch language versions, psychometric properties are described in the "measurement instruments" section. Subsequently, disease activity was measured and a submaximal exercise test performed. A trained rheumatology nurse performed disease activity measures in all patients and a trained physiotherapist with expertise in patients with RA performed all exercise tests. Patients were recruited from April to November 2009. The study was approved by the local medical ethics committee of Martini Hospital.

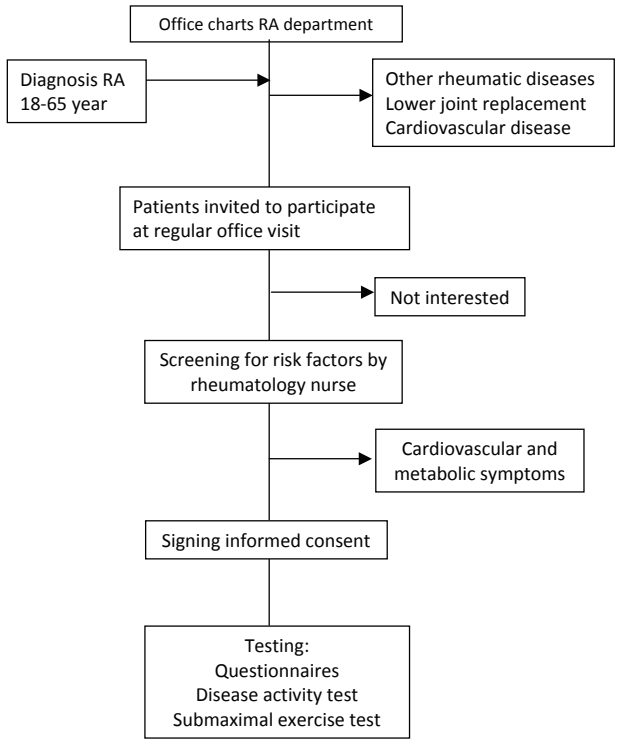

Fig. 1. Recruitment process April–November 2009.

Measurement instruments

Demographic and disease-related variables. The Arthritis Impact Measurement Scales 2 (AIMS2) was used to obtain demographic variables (age, gender, employment) and disease-related variables (disease duration, physical function and psychological status) (30). Disease activity was measured with the Disease Activity Score-28 (DAS28) (31).

The AIMS2 is designed to measure health status in a multidimensional fashion using 12 categories. These categories can be combined into a 3-component model of health status. The 3 components are: physical function (mobility level, walking and bending, hand and finger function, arm function, self-care tasks, household tasks), psychological status (level of tension, mood), and arthritis pain. In order to express these scores in similar units, a normalization procedure is performed. All scores are expressed in the range 0–10, with 0 representing good health status and 10 representing poor health status. The AIMS2 has good external validity and reliability is satisfactory (30). The internal consistency coefficients, Cronbach α, for the health status categories range from 0.66 to 0.89 (30).

The DAS28 combines single measures into an overall, continuous measure of RA disease activity (28 tender joint count, 28 swollen joint count, erythrocyte sedimentation rate (ESR), and a general health assessment on a 0–10 visual analogue scale). The range of the DAS28 is 0–9.4. The level of RA disease activity can be interpreted as low ($DAS28 \leq 3.2$), moderate ($3.2 < DAS28 \leq 5.1$), or as high disease activity ($DAS28 > 5.1$) (31). The DAS28 has good validity, it correlates well with the original DAS ($r > 0.94$) and test-retest reliability is good ($r = 0.8$) (31).

Dependent variable/outcome. Fatigue was assessed with the Multidimensional Assessment of Fatigue scale (MAF), which was developed to measure self-reported fatigue in adults with RA (23). The MAF

consists of 16 questions concerning the quantity, degree, distress, impact, and timing of fatigue. Questions 1–15 form the final score or Global Fatigue Index (GFI, range 0–50), whereas question 16 concerns change over the past week. The MAF has good concurrent validity, it correlates with the POMS fatigue subscale ($r = 0.84$), and good internal consistency (inter-item correlations 0.53–0.83, Cronbach's α 0.91–0.96) (32).

Independent variables. Depressive symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS). The HADS was developed to assess anxiety and depressive symptoms in a general medical population aged 16–65 years (33). There are 7 depression items measuring cognitive and emotional aspects of depression, predominately anhedonia, and 7 anxiety items that focus on cognitive and emotional aspects of anxiety. Somatic items relating to emotional and physical disorders are excluded. Scores in the Anxiety (HADS-A) and Depression subscale (HADS-D) range from 0 to 21. Higher scores indicate greater severity. The following recommended cut-off scores for the subscales were used: 0–7 considered non-case, 8–10 considered possible case, 11–21 considered probable case (33). The HADS has good construct validity. Internal consistency is good, Cronbach's α ranges from 0.82 to 0.90 for HADS-D.

Pain was assessed using the "Arthritis pain" component of the AIMS2 (30). The Arthritis pain component consists of one question to assess pain intensity and 4 questions assessing pain impact (days with pain, number joints with pain, stiffness, sleep disturbance due to pain).

Aerobic capacity was predicted using a single-stage submaximal walking test developed by Ebbeling et al. (34) for use with healthy adults. Minor & Johnson (35) assessed validity and reliability of this method to estimate aerobic capacity in women with RA. Criterion validity is good, correlation with maximal tests ranges from $r = 0.77$ to $r = 0.80$. Test-retest reliability is good, intraclass correlation coefficient (ICC) = 0.97 (95% confidence interval (CI) 0.94–0.99).

Following standardized instructions, participants walked on a treadmill (CompactGaitTM, Biometrics BV Almere, Netherlands) at a self-selected walking speed between 3.2 and 7.2 km/h at 0% grade. Warm-up was intended to elicit a heart rate (HR) between 50–70% of HRmax. Immediately after this 4-min warm-up the treadmill grade was increased to 5% and participants continued walking at the same speed for 4 more min. HR was measured continuously during the test using a handheld pulse oximeter (NPB-40, Nellcor Puritan Bennett LLC, Dublin, Ireland). Final HR and selected walking speed were entered into a previously developed equation (34) to estimate aerobic capacity: $VO_2max = 15.1 + 21.8 \times$ speed (mph) $- 0.327 \times$ HR (bpm) $- 0.26 \times$ speed $\times$ age (years) $+ 0.00504 \times$ HR $\times$ age $+ 5.98 \times$ gender (0 = female; 1 = male).

Physical activity level was assessed with the Short Questionnaire to Assess Health-enhancing PA (SQUASH) (36). The SQUASH assesses 4 PA categories: commuting activities, leisure-time activities (including sports), household activities, and activities at work and school. The time spent on PA per week was calculated for all categories by multiplying frequency (days/week) by duration (h/day). Intensity of activities was expressed in metabolic equivalent tasks (MET), using Ainsworths' compendium of PA (37). Total amount of PA was calculated as the sum of time × intensity × frequency per activity (METhours/week). The SQUASH is a fairly reliable ($r = 0.58$) and reasonably valid ($r = 0.45$) questionnaire (36).

Statistical analysis

The distributions of all variables were examined for normality. Mean and standard deviation (SD) was calculated for all normally distributed continuous variables, and median and range were calculated for continuous variables that were not normally distributed.

A backward multiple regression was performed to examine the unique role of PA and aerobic capacity in explaining variance in fatigue, with fatigue as the dependent variable and age, gender, pain, depressive symptoms, VO_2max and PA as the independent variables. Statistical significance level was set at $p \leq 0.05$. We calculated the statistical power for the study, with $\alpha = 0.05$, power = 0.8, 6 predictors (age, gender, pain, depressive symptoms, aerobic capacity and PA level) and estimated effect size = 0.3. This yielded a sample size of $n = 52$. The sample size of this study was set at 60 participants based on this sample size and an estimated 15% of incomplete data. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 17.0 for Windows, SPSS Inc., Chicago, USA).

RESULTS

A total of 44 women and 16 men with RA participated in this study. There were no missing data.

Participant characteristics are presented in Table I. Mean age of participants was 51.8 (SD 10.4) years and 43.3% were employed.

Disease duration ranged from 0 to 41 years and mean disease activity score was 3.4 (SD 1.4), which can be interpreted as moderate disease activity.

Participants reported a mean Physical function of 1.6 (SD 1.1) and a mean Psychological status of 3.1 (SD 0–8) on the AIMS2. Arthritis pain mean score was 4.1 (SD 2.0) and participants reported a median of 3.2 on HADS depressive symptoms. Total amount of PA in one week was a median of 176.9 (range 10.6–1,492.3) METhours/week. Male participants were more active than female participants: 307.2 METhours/week vs 129.6 METhours/week ($p = 0.01$). All participants completed the submaximal treadmill test. Mean VO_2max was significantly higher for male participants, 31.7 (SD 2.6) ml/kg/min vs 26.4 (SD 3.0) ml/kg/min for female participants ($p < 0.001$).

Table I. *Characteristics of study participants (*n*=60)*

Characteristics	
Age, years, mean (SD)	51.8 (10.4)
Women, %	73.3
Employed, %	43.3
Disease duration, years, mean (SD)	10.2 (0–41)
Physical function[a], mean (SD)	1.6 (1.1)
Psychological status[b], mean (SD)	3.1 (0–8)
Disease activity[c], mean (SD)	3.4 (1.4)
GFI[d], mean (SD)	20.3 (10.5)
1st quartile range	1.0–12.4
2nd quartile range	12.4–22.7
3rd quartile range	22.7–27.4
4th quartile range	27.4–45.2
Pain[e], mean (SD)	4.1 (2.0)
HADS-D[f], median (range)	3.2 (0–15)
HADS-A[g], median (range)	4.2 (0–16)
VO_2max, ml/kg/min, mean (SD)	27.8 (3.8)
HRtest[h], beats/min, mean (SD)	117 (12.2)
PA level, METhours/week, median (range)	176.9 (10.6–1,492.3)

Possible ranges: [a]0–10, higher indicates more disability. [b]0–10, higher indicates worse health status. [c]0–9.4, higher indicates more disease activity. [d]0–50, higher indicates more fatigue. [e]0–10, higher indicates more pain. [f]0–21, higher indicates more depressed. [g]0–21, higher indicates more anxious. [h]Heart rate measured at the end of the treadmill test.

GFI: Global Fatigue Index; HADS-D/HADS-A: Hospital Anxiety and Depression Scale; PA: physical activity; SD: standard deviation; HR: heart rate; MET: metabolic equivalent tasks.

Table II. *Intercorrelations of independent variables and Global Fatigue Index (GFI)*

	1	2	3	4	5	6	7
1 Gender	1	–0.084	–0.091	0.105	–0.630*	–0.321	0.000
2 Age		1	0.202	–0.123	–0.020	0.017	–0.209
3 Pain			1	0.381*	–0.089	–0.063	0.259*
4 HADS-D				1	–0.167	–0.043	0.576*
5 VO_2max					1	0.327*	–0.083
6 PA level						1	–0.087
7 GFI							1

*Statistical significance: $p \leq 0.05$.
HADS-D: Hospital Anxiety and Depression Scale (subscale depression); PA: physical activity.

The mean (SD) Global Fatigue Index (GFI) was 20.3 (10.5). As there is no universally accepted cut-off point to indicate severity of fatigue, we divided the scores into quartiles indicating light, moderate, severe and very severe fatigue, respectively (Table I). In 61.7% of participants intensity of fatigue was unchanged during the course of a week. During some, but not all, days of the week 48.3% of participants experienced fatigue, 18.3% experienced fatigue most of the time and 3% every day. Fatigue most often affected walking, doing household chores, and exercise other than walking. No statistically significant difference was found for GFI between males and females. Hierarchical multiple regression analysis was performed to examine the unique role of PA and aerobic capacity in explaining variance in fatigue when controlling for the influence of pain and depressive symptoms. Tests were conducted to check for violations of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Data for GFI were normally distributed; of the variables measured in this study only depressive symptoms had one outlier. Data were found to have been coded and entered correctly and the decision was made to retain the outlier. In reviewing the residual scatter plot no heteroscedasticity was noted. Data were reviewed for evidence of multicollinearity, statistically significant correlations ranged from 0.259 to –0.630. It was assumed that the variables were independent of each another (Table II).

Backward multiple regression showed a statistically significant relationship with depressive symptoms only ($t = 5.4$, $p < 0.001$), which explained 33% of variance of fatigue in patients with RA.

DISCUSSION

We hypothesized that low aerobic capacity capacity and PA are associated with fatigue, when controlling for age, gender, pain and depressive symptoms in persons with RA. In this study aerobic capacity and PA level made no statistically significant contribution in explaining the variance of fatigue as measured by the GFI. Depressive symptoms was the only variable with a unique statistically significant contribution, explaining 33% of the variance in fatigue in persons with RA.

Persons with RA rate fatigue as an important symptom interfering with their quality of life. In order to develop RA-specific interventions to enhance quality of life, it is important to understand specific factors contributing to fatigue. Findings that aerobic exercise has positive effects on fatigue suggest an association between deconditioning and fatigue (9). In this study mean VO_2max of participants was comparable to that of age-related healthy subjects and slightly younger patients with RA measured with the same treadmill test (34, 35). To determine level of PA METhours/week were used. The only study using the SQUASH (21) to determine PA level in patients with RA, measured PA in min/week. Patients in the present study were younger (51.8–60.5 years) and more active (2,339–1,535 min/week). PA was comparable to the general Dutch population. Our results do not appear to support the idea that patients with RA are fatigued due to lack of PA or aerobic capacity.

It is possible that the effect of aerobic exercise on fatigue is a result of the positive influence aerobic exercise has on depressive symptoms (14). In the present study depressive symptoms were highly correlated with fatigue. This is interesting, since patients experienced mild depressive symptoms. Two persons reached the cut-off point for a possible case (8 points) and 4 persons were considered probable cases (> 11 points) according to Zigmund & Snaith (33). The results are supported by findings of Huyser et al. (6), who found a unique contribution of depression (11%) in explaining the variance of fatigue. Depressive symptoms may express themselves as the inability to perform activities. We found no correlation between depressive symptoms and PA level. These findings are in contrast to results from Rupp et al. (3), who detected a moderate correlation of depression with reduced activity.

Although a correlation between pain and fatigue existed, $r = 0.259$ ($p = 0.023$), pain did not significantly contribute to the variance of fatigue. This finding seems to be in contrast with results from studies of Belza et al. (23) and Huyser et al. (6). In both studies level of pain was positively correlated with fatigue and explained 19% of the variance of fatigue. It is difficult to compare results because of differences in the use of measurement tools for pain and depressive symptoms. Disease activity and duration were not correlated with fatigue, which supports the idea that even with low disease activity people with RA are fatigued (7–10).

The fact that gender was not significantly associated with fatigue confirms earlier inconsistent findings. In the study of Reimsma et al. (13) and Wolfe & Michaud (26) gender was not a significant factor, while Belza et al. (23) found that gender significantly explained 13% variance of fatigue. They suggested that females were more fatigued, because they typically are responsible for household task. Jobs with no distinct end-points, such as housework, should produce more fatigue symptoms. Belza et al. (23) enrolled 75% female participants and fatigue particularly affected doing household activities. In the present study 73.3% of participants were female, mean GFI did not differ significantly between men and women (17.7–18.6; $p = 0.83$), and household activities was not the most affected activity.

Patients in the present study were younger and experienced less pain and disability than patients in comparable studies

(13, 30, 38). Disease duration was relatively short and disease activity moderate. In contrast to our findings, Lee et al. (9) found that exercising regularly was correlated with less fatigue. However, even GFI in exercisers was higher than in participants of the present study (24.3–18.1). In another study (12) exploring the effect of aerobic exercise on fatigue, participants had a comparable level of fatigue, but VO_2max was lower (22.7–28.1 ml/kg/min) than in the present study.

This study has several limitations. First, maximal exercise testing was rejected by the local medical ethics committee. Consequently, a submaximal exercise test and a multiple regression equation validated for people with RA were used. Multiple regression equations may be more accurate in predicting VO_2max than predictions using predicted maximal heart rate alone. Even so, there is evidence for this submaximal method to overestimate aerobic capacity in women with RA (35).

Secondly, disease severity and characteristics of participants may differ from other populations, although results were comparable to results of a 10-year follow-up study of patients with RA suggesting that health status is improving (38). Thirdly, due to the cross-sectional nature of this study, relations between depressive symptoms, PA level and fatigue could not be explored. In order to develop interventions to enhance quality of life of persons with RA, longitudinal research is needed to explore the manner in which these variables interact. Finally, the MAF scale is developed to explore 4 aspects of fatigue (degree, distress, impact, and timing). Fatigue is, however, expressed as the sum of these items and the potential to explore the complex character of fatigue and associations with different domains of quality of life are lost. Simple VAS fatigue scores show similar results in measuring the degree of fatigue compared with complex scales (39) and are easier to use. To obtain a more complete picture of fatigue and the relationships with RA, validation research on the use of the single domains of the MAF is required.

In conclusion, no relationship was found between aerobic capacity, level of PA and fatigue. This study confirms earlier results that depressive symptoms are associated with fatigue. Depression may result in decreased daily activities and increased fatigue. The relation between depression and deconditioning in RA remains unclear. The assumption that aerobic exercise decreases levels of fatigue in patients with RA as a result of increased aerobic capacity seems inaccurate. Future research should explore the effectiveness of interventions changing depressive symptoms in persons with RA and the correlation with level of PA and fatigue.

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