Deconditioning and fatigue in patients with rheumatoid arthritis

Master Thesis

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Are persons with rheumatoid arthritis deconditioned? a review of physical activity and aerobe capacity

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by polyarthritis and erosive synovitis and is associated with progressive impairments and activity limitations.[1, 2] The prevalence in the Dutch adult population is approximately 1% and women have a three times higher risk of developing RA[3]. Although most of the symptoms of RA are located in the joints it also produces general symptoms such as fatigue[4]. In the literature, a consensus definition for fatigue is not presented. 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 higher levels of fatigue compared to the general population and fatigue predicts decreased vitality and loss of physical and social functioning[3]. Experiencing fatigue may have a negative impact on physical activity and exercise because there is less energy to expend[4]. Duration and intensity of activities may be reduced and motivation to plan a next exercise session decreased. This, in turn, can lead to a cycle of deconditioning that results in loss of physical fitness and a higher level of exertion when conducting activities of daily living[8]. Exercise restrictions, traditionally given to patients with RA because of concerns about aggravating joint inflammation and accelerating joint damage, may have led to inadequate levels of physical activity and deconditioning[9]. It is therefore possible that fatigue is part of the deconditioning cycle and not so much a predictor of physical fitness. The American College of Rheumatology (ACR) now recommends regular participation in dynamic exercise programs[10]. Research concerning PA focuses mainly on regular exercise[11-13] and states that persons with RA do not exercise and are therefore inactive. Little is known about the level of daily physical activity (PA) among persons with RA. Since the general guideline to maintain health only recommends moderate-intensity PA of at least 30 minutes, on 5 days a week[11, 14]. The term physical activity is broader than exercise and it is interesting whether individuals with RA are less physically active and experience a decreased aerobe capacity.

The aim of this review was to compare the daily PA level and aerobe capacity of persons with RA with those of a healthy reference population.

Materials and Methods

Literature Search

Electronic databases Medline, Cinahl, Embase, Cochrane and PsycINFO were systematically searched up to October 2008 using the following Mesh terms and text words: (motor activity OR leisure activities OR human activities OR activities of daily living OR aerobic capacity OR energy expenditure) AND rheumatoid arthritis AND healthy, to find studies comparing patients with RA to healthy persons. In order to limit results to adults, the restriction NOT (child OR adolescent) was added. Reference lists from included studies were searched manually for additional relevant studies. The full search strategy is available on request from the corresponding author.

Inclusion criteria

Studies were included for review when following criteria were met.

- the target population consisted of adults with RA (18 years and older)
- physical activity, energy expenditure or aerobic capacity were outcome measures
- at baseline the outcome measures were compared to those of healthy controls and values and measures of variability were described

Exclusion criteria

- single case reports
- studies describing a direct post operative situation
- studies written in any language other than English, German or Dutch

Definitions

The term 'physical activity' is defined as: "Any bodily movement produced by skeletal muscles that results in a substantial energy expenditure"[15].

'Energy expenditure' is defined as energy expended during physical activity and measured in calories or joules per unit of time[16].

Aerobe capacity is defined as the ability to deliver oxygen to the exercising muscles and to utilize it to generate energy during exercise and therefore depends on the pulmonary, cardiovascular and haematological components of oxygen delivery and the oxidative mechanisms of the exercising muscle. Maximal oxygen uptake

(VO_2max) is the highest amount of oxygen consumed during maximal exercise in activities that require the use the large muscle groups in the legs, or arms and legs combined[16] and is recognized as the best single measure of adults' aerobic fitness. Using the above mentioned criteria, a researcher (TM) reviewed the titles of articles in the search printouts from the databases. Abstracts from potentially relevant studies were red and included when all criteria were met. After full text reading articles were finally included when all afore mentioned criteria were met. A manual search of references from included studies was conducted to retrieve further potentially relevant studies.

Assessing trial characteristics and outcome data

The following information was systematically extracted by reviewers TM and HW: type of study, number of participating patients with RA, sex, age, setting, body composition, disease duration, classification of impairment, use of medicines and outcome measures.

Based on consensus extracted data were included in the review.

Quality assessment of studies

Although a commonly accepted valid rating instrument concerning the quality assessment of observational studies does not yet exist, there appears to be consensus about important items[17-19]. This review focuses on differences between persons with RA and healthy controls in PA in daily routine. In the case of intervention studies a comparison of patients and controls at baseline was used. This results in the following assessment items: selection of patients and controls, sample size calculation, adjustment for confounding, blinding of assessors and use of statistical analysis.

Results

The literature search yielded 148 studies, from which nine double hits were excluded. Another 47 studies were excluded based on the title. The abstracts of 92 studies were assessed, of these 92 studies 79 studies were excluded because they did not met the inclusion criteria. Finally 13 studies were retrieved for full text reading, which resulted in the exclusion of another article because no data concerning afore mentioned outcome measures was given. References tracking of the included

studies did not yield new studies. Finally 12 studies were included. Results of the literature search and reasons for exclusion are depicted in Figure 1.

Quality assessment

The included studies were all observational studies: ten cross-sectional studies, and two cohort studies. Six studies included small groups of patients[20-25] in which sample size varied from 8 to 35 patients, the other six studies[26-31] included larger samples, sample size ranged from 67 to 232 patients.

In only seven studies[20, 22-25, 28, 29] samples of patients and controls were of equal size, in the remaining 5 studies group sizes differed significantly[21, 26, 27, 30, 31]. The majority of the patients were recruited from rheumatology or arthritis clinics, once from a rehabilitation centre[22] and in two cases[26, 27] the recruitment method was unclear. Concerning the recruitment of controls no information was available in six of the studies[20, 22-25, 27]. Four times healthy persons living in the same area were used[20, 26, 28, 29], once healthy relatives acted as controls[30] and one study used information from the general Dutch population as a reference group[31].

Information about matching of patients and controls was reported in nine studies [20-22, 24-28, 30]. Different combinations of the following factors were used: race[24, 25], age[20-22, 24-26, 28], gender[20, 22, 24, 26, 28] and body composition[20, 24, 25]. Once groups were matched on genetic and ethnic values[30] and once controls were included to contrast with patients in terms of level of PA and body composition[27]. Having a sedentary lifestyle was also a criterion to match patients and controls in three[20, 22, 23] of the five studies[20-23, 26] investigating aerobe capacity, whereas one study[21] included physically active patients and controls.

Three studies mentioned conducting sample size calculations[22, 25, 31]. Sample sizes were inadequate with regard to statistical analysis in two cases[22, 31] and in the third study[25] adequacy of the sample size was not mentioned. None of the studies mentioned blinding of assessors and six studies[20, 22-25, 30] reported that data were tested for the assumptions for parametric statistical tests or justified the use of non-parametric tests.

Patient characteristics

All patients met ACR criteria for RA[32] and were classified into Functional Class I – IV (mild to severe impairment)[33]. In two studies patients were classified as Functional

Class II[22, 26], in five studies patients with different levels of Functional Class (FC) were combined in the study population[20, 21, 23, 24, 30] while no information on level of impairment was given in the remaining five studies[25, 27-29, 31].

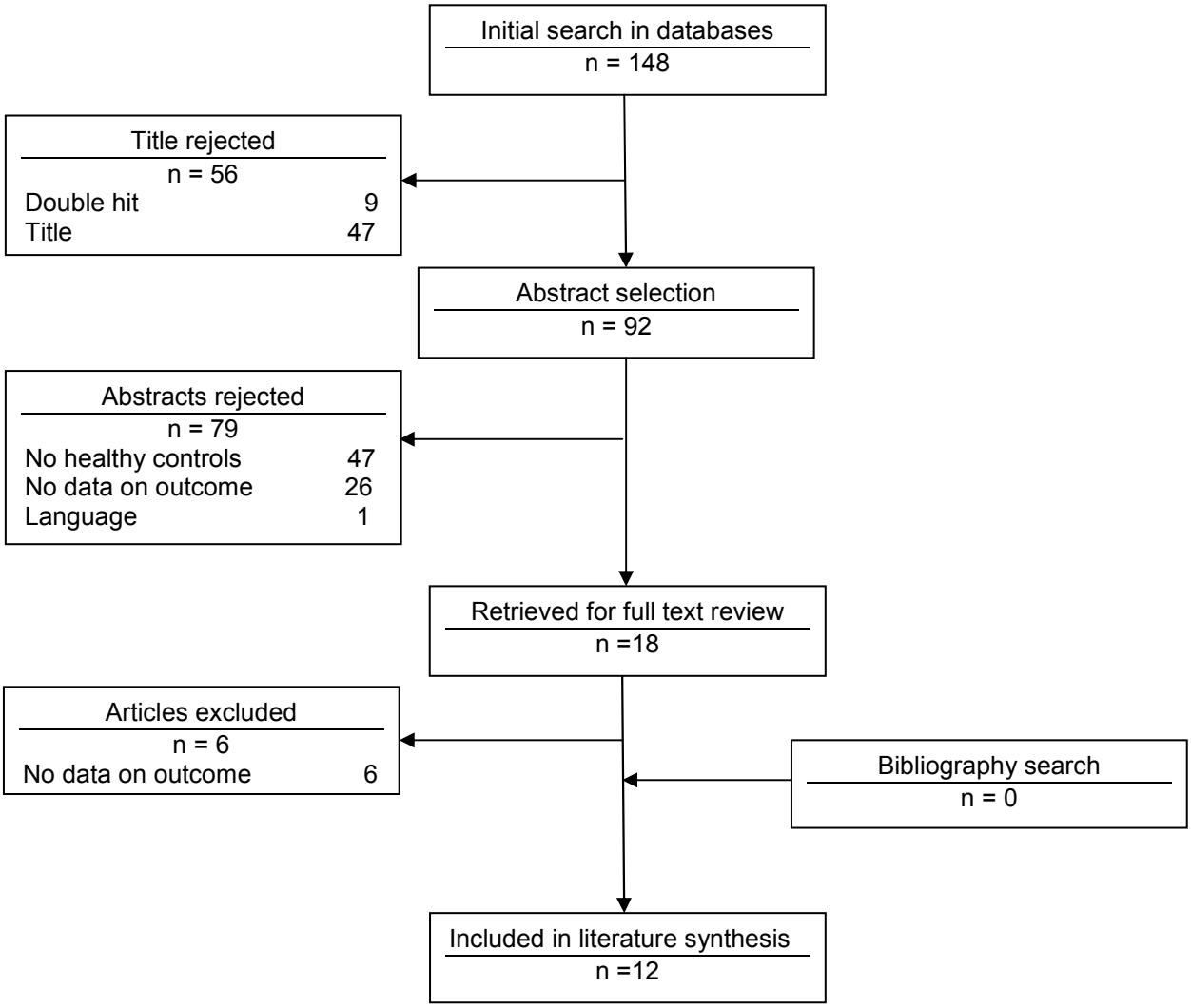

Fig.1. Summary flow chart of article selection process

Most studies predominantly used female participants, with percentages ranging from 62,5% to 88,6%. In three studies only women were included[21, 25, 30] and in one study gender of participants was unknown[22]. The mean age of patients ranged from 38.1 years to 62.6 years. The use of anti rheumatic drugs and analgesics was described in eight studies[21-26, 29, 30]. In the six studies[20, 22, 23, 25, 29, 30] patients were excluded because of severe cardiac and pulmonary diseases[20], or because they used a walking aid[25].

In three studies[22, 29, 30] participants with co morbidity other than cardio-pulmonary disease were excluded. One study used a body mass index above 30 as an exclusion criterium[23] and participants who exercised regularly were also excluded once[25]. Characteristics of patients and controls, disease parameters and results on energy expenditure and physical activity are presented in Table 1. Characteristics of patients and controls, disease parameters and results on aerobe capacity are presented in Table 2.

Energy expenditure in physical activity

EEPA can be calculated using the following equation: EEPA =TEE − REE –TEF, wherein TEF stands for the thermal effect of food[16]. Three studies that measured resting energy expenditure (REE), by indirect calorimetry, described similar values of REE in patients with RA and their healthy controls[23-25], even when results were adjusted for body cell mass and weight[25]. However when results were adjusted for percentage body fat, REE was higher in persons with RA compared to controls[23, 24]. To calculate energy expenditure in physical activity (EEPA) total energy (TEE) consumption was measured, using the doubly labelled water technique (DLW) in one study[25]. In the same trial energy expenditure in PA was estimated using a PA questionnaire and with a physical activity monitor. Using al three forms of measurement EEPA was found to be significantly lower in persons with RA compared to controls. Results from the calculated EEPA correlated with results obtained with the physical activity monitor (r = 0.37) but not with the PA questionnaire, however.

Physical activity level

Six studies[24, 27-31] used questionnaires to assess physical activity level. Physical activity in patients with RA was assessed by measuring different intensity levels, time spent on PA or questionnaires were used to calculate EEPA.

Classifying PA based on levels of intensity was done in two studies[27, 30]. Using a modified Physical Activity Scale to quantify PA undertaken during a normal week, patients with RA were found to be less engaged in moderate or intense recreational activities or sports[27]. When levels of PA were classified into levels of activity (sedentarism, mild, moderate or intense activities)[30], patients participated on a lower intensity level compared to a reference group. The patients did not engage in regular

exercise and were identified to be 15% more sedentary compared to controls. Information concerning the used instrument remained unclear.

Measuring hours per day spent in light, moderate or vigorous forms of PA was done using a Paffenbarger questionnaire[24]. Physical activity was assessed as time spent on leisure activities such as walking, stair climbing and sport and converted into energy spent per week. In another study[28] time spent on PA was recorded during one week using an occupation log consisting of 10 different activities collapsed into 3 categories: work, activities of daily living (ADL) and leisure. Finally the Short Questionnaire to Assess Health Enhancing PA (SQUASH) was used to estimate time spent on light, moderate and vigorous activities in a period of seven days[31]. Physical activity is categorised as commuting activities, leisure time activities, household activities, and activities at work and school. Results showed that the proportion of patients with RA meeting the public health recommendation for PA equals that of the general public (58%), nevertheless younger patients (45 – 65 years) were less active in all categories than controls. Older patients (> 65 years) showed only a significant difference in moderate PA compared to the reference group[31].

Contrary to the previous statement other results showed that patients with RA spent an equal amount of time on PA compared to controls[24, 28]. However, patients spent more time on light activities[24] and if PA was categorized as ADL, leisure and work, patients spent more time on ADL while spending less on work[28].

Modified versions of the Paffenbarger Physical Activity Questionnaire (PPAQ) were used in two trials[25, 29] to calculate energy expenditure in PA. Though similar proportions of patients and controls met recommended minimum levels of energy expenditure, patients with RA expended less energy in PA (24.7%), mainly due to walking less (33.7%)[29]. Roubenoff et al.[25] found comparable amounts of mean decreased energy expenditure on PA in patients with RA (30.5%). Both studies gave no information on the way the questionnaire was modified and the consequences for PA assessment.

Aerobe capacity

Aerobe capacity was examined in five studies. Two studies used a maximal treadmill test[20, 22]. A maximal bicycle test was used in two studies[21, 23] and one study used a sub-maximal bicycle test[26].

The first study used an increasing-load protocol to measured VO_2 at every stage of the treadmill test[20]. The protocol was continued until predicted maximal heart rate was reached (220 b/min – age). The second study[22] used the 'Bruce' increasing-load protocol to measure aerobic capacity in a treadmill test. Aerobic capacity was defined as VO_2peak. Ten minutes after reaching anaerobic threshold all participants were stopped and VO_2 was measured. Both studies measured oxygen uptake using the breath-by-breath method. In both cases no significant differences in aerobe capacity between patients and controls were detected.
The first study[20] compared patients and controls at the end of the last stage to determine VO_2max. However, 50%, 60% and 100% of patients of FC I, II and III respectively, dropped out before reaching the final stage of the test.
Energy expenditure at sub-maximal levels was higher in patients of FC II than in the control group, a difference that was not found when comparing patients of FC I with the control group. No statistical test was applied to detect differences between FC III and controls due to the small number of patients of FC III.

Both studies[21, 23] that conducted maximal bicycle tests used an increasing-load protocol. In the first study[21] the test was continued until voluntary exhaustion, however, no definition of VO_2max was given. In the other study[23] VO_2max was defined as reaching one of the following three criteria: O_2 plateau, respiratory exchange ratio > 1.0, or heart rate within 10% of expected goal. In the study of Hakkinen et al.[21] patients with early RA (mean disease duration 2.9 years) or long-term RA (mean disease duration 14.5 years) were compared with healthy peers. At the end of the test mean maximal heart rate of participants fell within 5% of predicted maximal heart rate and no significant differences between VO_2 max of early RA, long-term RA or control group were found.
In the study by Rall et al.[23] patients with RA (mean age 41.8 years) were compared to groups of young and elderly controls. Persons with RA had a lower mean VO_2max compared to the young controls (mean age 25.8 years). Whereas aerobic capacity of patients and elderly controls (mean age 69,5 years) did not differ significantly.
Finally, aerobic capacity was predicted using an Åstrand protocol during a bicycle test[26].
Participants were divided in two categories (younger and older than 54 years) and bicycle test results were compared between males or females with RA and healthy

controls. Persons with RA had lower aerobic capacity compared to healthy control groups. Females had lower VO_2max than males and VO_2max decreased with age in all participants.

Discussion

The aim of this review was to explore whether individuals with RA are less physically active and experience a decreased aerobe capacity, compared to healthy peers. Few studies were available that compared daily PA between persons with RA and healthy control groups. Studies exploring aerobe capacity of persons with RA and healthy controls were even more scarce.

Evidence that daily PA is lower in persons with RA compared to healthy controls is subjective, due to heterogeneity in assessment methods and methodological issues. Only one study[25] used doubly labelled water, the objective measure, to assess PA. The questionnaires used in the other studies all assess PA differently. Information on actual level of PA may be incomplete and results of studies are not comparable. Questionnaires used in these studies are developed for use in healthy populations and consequences for the results are unknown.

Evidence that aerobe capacity is reduced in persons with RA compared to healthy controls is inconclusive. Four studies investigating aerobe capacity with a maximal exercise test detected no significant difference between VO_2max of patient and controls. This may be due to methodological issues, such as small sample sizes[34] or definition of VO_2max.

Reference groups differed between studies and the choice of the reference group may also have influenced the observed differences. Except for the study of Tourinho et al.[30] who used relatives, controls were volunteers who were matched with the RA group on limited factors such as age, gender or BMI. Little or no information was given concerning employment, behavioural factors or attitudes influencing PA and aerobe capacity. Five studies used unequal sample sizes for patients and controls, this may have compromised matching[34].

The reviewed studies included persons with different lifestyles and some studies included patients and controls with different lifestyles. No clear definitions were given of “physically active” or “sedentary lifestyle”. Finally, the amount of information that was equally described in studies was limited. Therefore comparing results was only possible on age and gender.

Physical activity level

The best reference method to estimate energy expenditure in humans during daily life is the doubly labelled water method (DLW)[35]. Roubenoff et al.[25] combined the use of DLW and a questionnaire to calculate energy expenditure in PA. Energy expenditure in PA and the physical activity level, defined as total energy expenditure divided by resting, was lower in patients than controls. However, the energy expenditure of patients in this study was comparable to that of healthy peers[1]. Healthy controls seemed more active rather than patients being inactive.

When results of DLW and the questionnaire were compared, results did not correlate. This might demonstrate that the questionnaire does not accurately reflect energy expenditure in PA. Questionnaires using a standard intensity categorization of PA might underestimate energy expenditure of patients with RA. These questionnaires assess energy expenditure based on metabolic equivalent values (MET) defined by a compendium of PA and are developed for use in a healthy population. Patients in the trial of de Caravalho et al[20]. expended significantly more energy than healthy controls, up to 17,9% especially at walking speeds (3-5 km/h)[20]. Therefore a diminished energy expenditure of 24% found by Mancuso et al.[29], mainly caused by less walking may be inaccurate[29].

Some researchers suggest that one third of persons with RA experience cachexie[24, 36], defined as a loss of muscle mass combined with higher fat mass and higher REE. Matching persons with RA and healthy controls on BMI and comparing energy expenditure based on METs may therefore lead to a biased result.

McKinnon et al[28] found that patients were 20% less physically active. The difference was caused by less time spent on work. This may be due to the fact that patients were less employed compared to healthy controls: 43% - 86%[28]. Tourinho et al. reported similar differences: 17.3% - 96.7%[30]. These results are similar to that from a review of Geuskens et al.[37]. They stated that patients with RA are at risk to become unemployed with increasing age and disease duration. Three studies gave no information on employment status of participants[24, 25, 31]. It is possible however that differences in PA level found in these studies were mainly caused by differences in the degree of employment of patients and controls. Mean age of patients was 50, 47 and 62.6 years[24, 25, 31], respectively and they all had long-time RA. Due to lack of

information It remains unclear if unemployment was caused by RA and responsible for diminished levels of PA. When PA level of persons with RA was compared to data from the Dutch population patients were less active. However, employed patients and controls showed comparable levels of PA (2577 min/wk vs 2433 min/wk)[31].
Mancuso et al.[29] included only patients and controls who were employed at the start of the trial. Still they found a mean difference in energy expenditure in patients and controls of 24.7%. In this study the Paffenberger Index was used to assess PA. Walking, stair climbing and sport are converted in expended energy per week. Differences in results compared to other studies may have occurred because time spent at work is not specifically assessed in this scale.
Physical activity is both a behavioural characteristic and a physiological attribute. Behavioural factors that predict higher levels of PA in a healthy population are: higher self-efficacy in the ability to participate in PA, a stronger belief in the benefits of PA and greater social support to participate in PA[12]. Research shows that combined with attitudes toward the disease the same factors apply to patients with RA[12, 38]. In the study of Ekdahl et al.[26] patients with RA had a lower aerobe capacity and were less active than healthy controls. Results highly correlated with participants attitude to the importance of exercise. These findings are also supported by Eurenius et al.[11] who detected only a low correlation between self reported level of PA and aerobe capacity and suggested that behavioural factors should be included in research.
These factors should be clearly described to enhance comparability. For instance, Ekdahl et al.[26] and Hakkinen at al.[21] both included physically active controls. The controls (< 54 years) in the first study had a higher mean value of VO_2max (31,7 ml/kg/min) compared to controls (mean age 41 years) in the second study (24,8 ml/kg/min). It is possible this was due to differences in activity levels.

Aerobe capacity

Using maximal tests no significant differences in aerobe capacity were detected between persons with RA and healthy peers, this may be due to small sample sizes[34]. Two studies used sedentary persons as controls[20, 22]. Kurtais et al.[22] did not define sedentary, whereas de Carvalho et al.[20] defined sedentary as non-exercising. Hakkinen et al.[21] included physically active women, who exercised 3 – 4 hours / week. Still values of VO_2max were comparable in all studies. The small samples

combined with large heterogeneity of participants in age and possibly in lifestyle may have compromised the power of the studies[34].
Test results may also be biased because it is unclear whether participants reached maximal heart rate (max HR). Maximal HR of patients in the study of de Carvalho was significantly lower compared to controls and just reached 90% of predicted max HR. Participants in the study by Kurtais[22] were all stopped 10 minutes after reaching the anaerobic threshold. Although not statistically significant, mean max HR of patients was lower than of controls and did not reach 90% of predicted max HR. Maximal HR remained lower in patients with long-time RA (LRA) compared to persons with early RA (ERA) and controls[21]. Maximal HR was within 10% of predicted max HR in all groups. Fitness level of patients and controls could be regarded as fair, compared to normative data[16].

When aerobe capacity was predicted by conducting a sub-maximal bicycle test[26] patients VO_2max was decreased compared to controls. At baseline controls were more active and exercised more frequently compared to persons with RA. Results may be biased because sub-maximal tests of less fit people tend to underestimate observed values[16]. Minor et al[39, 40] also showed that the correlation of predicted VO_2max and measured VO_2max diminished from 0.96 to 0.77 when a sub-maximal treadmill test, validated for use in a healthy population, was used for testing patients with RA.

The reviewed studies included patients according to functional class. In most cases the sample consisted of a mixed group[20-23]. In the study that described results for separate functional classes[20], VO_2max decreased from FCI to FCIII and sub-maximal energy expenditure was higher in FCII and FCIII compared to FCI and controls. Participants in FCII and FCIII experienced a higher level of disability compared to FCI and healthy controls which is in accordance with the revised functional class criteria[33]. When aerobe capacity of persons with ERA and LRA was compared, persons with LRA experienced more disability[21]. Aerobe capacity in persons with ERA tended to be higher than persons with LRA and controls. In this study patients in FCI and FCII were included. Although no information was available it is plausible that, since people with LRA experienced more disability, more persons in FCII were allocated in de LRA group.

This literature review has certain limitations. Although a literature search was conducted in multiple databases and reference tracking performed, only studies written in English, German or Dutch were included. Literature published in journals not indexed in electronic databases was not included, this may have led to biased results[41]. Tricco et al[41]. state that it still has to be explored if having two people independently screen potentially relevant material, as is usual in conducting an systematic review, does in fact decrease bias. Still, bias may have occurred in the process of including studies in this review since it was done by one researcher.

Conclusion

Persons with RA are less engaged in regular exercise and intense leisure activities. Due to heterogeneity in used instruments to assess physical activity and sampling issues such as employment status it is not possible to conclude that daily physical activity is lower in persons with RA compared to healthy controls. Unemployment seems to contribute to diminished activity level, future research on physical activity should incorporate employment status and the correlation with RA.

The results of this review do not support the conclusion that persons with RA have a decreased aerobic capacity compared to healthy controls. When results are compared to sex and age related normative data, both patients and controls have an aerobic capacity below average. This may reflect the fact that inactivity is present in half the general population. Research should take into account behavioural factors that relate to PA and determine if there is a unique relation to RA.

A higher functional class seems to be related to higher sub-maximal energy expenditure and lower levels of PA and aerobe capacity. Future research should differentiate between patients of different functional classes to explore consequences of these differences.

Reference List

(1) Plasqui G. The role of physical activity in rheumatoid arthritis. Physiol Behav 2008 May 23;94(2):270-5.
(2) van der Heijde D. Impact of rheumatoid arthritis on physical function during the first five years. No longer a question mark? Rheumatology (UK) 2000;39(6):579-80.
(3) Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Rheum 2004 August 15;51(4):578-85.
(4) Belza B. The impact of fatigue on exercise performance. Arthritis Care Res 1994 December;7(4):176-80.
(5) Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res 2004 February;56(2):157-70.
(6) Huyser BA, Parker JC, Thoreson R, Smarr KL, Johnson JC, Hoffman R. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998 December;41(12):2230-7.
(7) Repping-Wuts H, Fransen J, van AT, Bleijenberg G, van RP. Persistent severe fatigue in patients with rheumatoid arthritis. J Clin Nurs 2007 November;16(11C):377-83.
(8) Evans WJ, Lambert CP. Physiological basis of fatigue. Am J Phys Med Rehabil 2007 January;86(1 Suppl):S29-S46.
(9) Mayoux-Benhamou A, Giraudet-Le Quintrec JS, Ravaud P et al. Influence of patient education on exercise compliance in rheumatoid arthritis: a prospective 12-month randomized controlled trial. J Rheumatol 2008 February;35(2):216-23.
(10) Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercises in the management of rheumatoid arthritis in adults. Phys Ther 2004 October;84(10):934-72.
(11) Eurenius E, Stenstrom CH. Physical activity, physical fitness, and general health perception among individuals with rheumatoid arthritis. Arthritis Rheum 2005 February 15;53(1):48-55.
(12) Greene BL, Haldeman GF, Kaminski A, Neal K, Lim SS, Conn DL. Factors affecting physical activity behavior in urban adults with arthritis who are predominantly African-American and female. Phys Ther 2006 April;86(4):510-9.
(13) Sokka T, Hakkinen A, Kautiainen H et al. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. Arthritis Rheum 2008 January 15;59(1):42-50.
(14) Wilson PW, Paffenbarger RS, Jr., Morris JN, Havlik RJ. Assessment methods for physical activity and physical fitness in population studies: report of a NHLBI workshop. Am Heart J 1986 June;111(6):1177-92.
(15) Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985 March;100(2):126-31.
(16) McArdle WD, Katch FI, Katch VL. Exercise physiology. sixth edition ed. Lippincott Williams & Wilkins; 2007.

(17) Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F. Evaluating non-randomised intervention studies. Health Technol Assess 2003 September;7(27).
(18) Mallen C, Peat G, Croft P. Quality assessment of observational studies is not commonplace in systematic reviews. J Clin Epidemiol 2006 August;59(8):765-9.
(19) West S, King V, Carey TS et al. Systems to rate the strength of scientific evidence. Evid Rep Technol Assess (Summ) 2002 March;(47):1-11.
(20) de Carvalho MR, Tebexreni AS, Salles CA, Barros NT, Natour J. Oxygen uptake during walking in patients with rheumatoid arthritis--a controlled study. J Rheumatol 2004 April;31(4):655-62.
(21) Hakkinen A, Haanonan P, Nyman K, Hakkinen K. Aerobic and neuromuscular performance capacity of physically active females with early or long-term rheumatoid arthritis compared to matched healthy women. Scand J Rheumatol 2002;31(6):345-50.
(22) Kurtais Y, Tur BS, Elhan AH, Erdogan MF, Yalcin P. Hypothalamic-pituitary-adrenal hormonal responses to exercise stress test in patients with rheumatoid arthritis compared to healthy controls. J Rheumatol 2006 August;33(8):1530-7.
(23) Rall LC, Meydani SN, Kehayias JJ, wson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum 1996 March;39(3):415-26.
(24) Roubenoff R, Roubenoff RA, Cannon JG et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 1994 June;93(6):2379-86.
(25) Roubenoff R, Walsmith J, Lundgren N, Snydman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. American Journal of Clinical Nutrition 2002 October;76(4):774-9.
(26) Ekdahl C, Broman G. Muscle strength, endurance, and aerobic capacity in rheumatoid arthritis: a comparative study with healthy subjects. Ann Rheum Dis 1992 January;51(1):35-40.
(27) Lemmey A, Maddison P, Breslin A et al. Association between insulin-like growth factor status and physical activity levels in rheumatoid arthritis. J Rheumatol 2001 January;28(1):29-34.
(28) MacKinnon JR, Miller WC. Rheumatoid Arthritis and Self Esteem: The Impact of Quality Occupation. J Occupational Sc 2003 August;10(2):90-8.
(29) Mancuso CA, Rincon M, Sayles W, Paget SA. Comparison of energy expenditure from lifestyle physical activities between patients with rheumatoid arthritis and healthy controls. Arthritis Rheum 2007 May 15;57(4):672-8.
(30) Tourinho TF, Capp E, Brenol JC, Stein A. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: A cohort study. Rheumatol Int 2008;28(10):1001-7.
(31) van den Berg MH, de B, I, le CS, Breedveld FC, Vliet Vlieland TP. Are patients with rheumatoid arthritis less physically active than the general population? J Clin Rheumatol 2007 August;13(4):181-6.
(32) Arnett FC, Hunder GG, et al. The American Rheumatism Associatio 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheum 1988;Vol. 31(no. 3):315-24.

(33) Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992 May;35(5):498-502.
(34) Portney LG, Watkins MP. foundations of clinical research, applications to practice. second edition ed. Prentice Hall Health; 2000.
(35) Pols MA, Peeters PH, Kemper HC, Grobbee DE. Methodological aspects of physical activity assessment in epidemiological studies. Eur J Epidemiol 1998 January;14(1):63-70.
(36) Metsios GS, Stavropoulos-Kalinoglou A, Douglas KM et al. Blockade of tumour necrosis factor-alpha in rheumatoid arthritis: effects on components of rheumatoid cachexia. Rheumatology (Oxford) 2007 December;46(12):1824-7.
(37) Geuskens GA, Burdorf A, Hazes JM. Consequences of rheumatoid arthritis for performance of social roles--a literature review. J Rheumatol 2007 June;34(6):1248-60.
(38) Eurenius E, Biguet G, Stenstr+Âm CH. Attitudes toward physical activity among people with rheumatoid arthritis. Physiotherapy Theory & Practice 2003 March;19(1):53-62.
(39) Ebbeling CB, Ward A, Puleo EM, Widrick J, Rippe JM. Development of a single-stage submaximal treadmill walking test. Med Sci Sports Exerc 1991 August;23(8):966-73.
(40) Minor MA, Johnson JC. Reliability and validity of a submaximal treadmill test to estimate aerobic capacity in women with rheumatic disease. J Rheumatol 1996 September;23(9):1517-23.
(41) Tricco AC, Tetzlaff J, Sampson M et al. Few systematic reviews exist documenting the extent of bias: a systematic review. J Clin Epidemiol 2008 May;61(5):422-34.

Table 1: Studies comparing level of physical activity in RA patients and a healthy reference population

study	n (% F)	Reference population n (%F)	Patients with RA: Setting	Age [range]	Body Compostion	Disease duration	Impairment (FC I-IV)	Physical activity RA patiënts versus reference population p: significant difference	
v d Berg 2007*	232 (71.1%)	6,428,441 (53%) GP records	Hospital based	62.6 (9.2) 45-64 jr: 58%	?	?	?	Light: 1297±1009 min/wk / 1495 min/wk Moderate: 369±543 min.wk / 517 min/wk Vigorous: 170±257 min/wk / 187 min/wk	p=0.01 p=0.01 p=0.01
				> 65 jr: 42%				Light: 634±795 min/wk / 618 min/wk Moderate: 231±244 min/wk /304 min/wk Vigorous: 250±417 min/wk / 296 min/wk	p=0.01
Lemney♦ 2001	73 (63.0%)	28 (57%) ?	?	52.9 (12.9)	Fat 36.6 (12.8) % p<0.001	?	?	Physical Activity Scale (0-7) 0.8±0.7 / 5.4±1.7	p<0.001
Mancuso 2007	121 (84%)	120 (91%) Personnel hospital	Hospital based	49 [19-72]	?	14 (10)	?	Walking: 692±610 kcal/w / 1.044±1260 kcal/w Stair climbing: 184±212 kcal/w / 185±262 kcal/w Exercise: 599±848 kcal/w / controls: 729±1210 kcal/w	p=0.002
MacKinnon ♥ 2003	143 (74.8%)	142 (72.5%) area residence	Rheumatology clinic	49.7 (11.2)	?	?	?	Work 37.1±19.6 h/wk / 46.5±17.2 h/wk ADL 89.0±15.3 h/wk / 81.1±11.5 h/wk Leisure 38.4±15.4 h/wk / 37.9±15.6 h/wk	p<0.05 p<0.05
Roubenoff♣ 2002	20 (100%)	20 (100%) ?	Arthritis center	47 (14)	BMI 25.3 (4.5)	7.7 (6.5)	FCI FCII	EEPA 2849±1075 kJ/d / 3883±1732 kJ/d PA questionnaire 2188±1075 kJ/d / 3150±1611 kJ/d PA activity monitor 1264±992 kJ/d / 2280±1469 kJ/d	p<0.04 p<0.04 p<0.04
Tourinho♠ 2007	71 (100)	29 (100) sisters / cousins	Rheumatology clinic	38.10 (6.62)	1.57 (0.14) m 62.68 (12.56) kg	30 (7,3)	FC I: 70%	Sedentarism 17.3 % / 3.4% Mild 57.7% / 35% Moderate 25% / 65% Intense 0% / 0% No exercise in leisure time 74% / 66.7%	p=0.004 p=0.004
Roubenoff◊ 1994	23 (82.6)	23 (82.6) ?	Rheumatology clinic	50 (15)	Body cell mass 22.5 (4.3) kg p< 0.000	12.3±8.4 jr	FC I (n=5) FC II (n=10) FC III/IV (n=8)	Vigorous 0.1±0.2 h/d / 1.5±1.5 h/d Moderate 4.0±3.2 h/d / 5.6±2.3 h/d Light 11.6±3.4 h/d / 9.2±3.2 h/d	p<0.0001 p<0.06 p<0.02

Age, body composition,disease duration and physical activity are expresed as mean±standard deviation if not expressed otherwise. n: number of participants with RA or in reference population, RA: rheumatoid arthritis, FC: Functional Class, GP: general population, BMI: body mass index in kilogram per square meter, >: older than.
kcal/wk: kilocalory per week, min/wk: minutes per week, kJ/d: kiloJoule per day, h/d: hours per day. Controls matched on ♣: race, age, body mass index, ♠: genetic factors, ♥: age, sex, ◊: race, age, sex, weight, ♦: controls selected to contrast on body fat, activity level, *: no information on matching

Table 2 : Studies comparing level of aerobe capacity in RA patients and a healthy reference population

Study	n (% F)	Reference Population n (% F)	Patient characteristics: Setting	Age [range]	Body Composition	Disease duration	Impairment (FC I-IV)	VO_2max RA patients versus reference population (ml/kg.min) p: significant difference	
de Carvalho 2003♣ MT	35 (88.6%)	35 (?) hospital staff	Rheumatology clinic	47,85 (8,29)	?	8	FCI: 40% FCII: 51% FCIII: 8.6%	FC I: 24.89 (n=7) FC II: 21.86 (n=6) / 24.28 (n=22)	NS
Ekdahl 1992♥ SMB	67 (62.7%)	77 (61.0%) personnel	?	53.0 (10.2)	female: 164.1 (5.6) cm female: 66.1 (11.6) kg male: 177.9 (6.8) cm male: 75.6 (10.7 kg	10.6 (7.8)	FCII	female younger than 54 jr: 22.3±6.8 / 31.7±12.1 older than 54 jr: 18.7±3.5 / 21.9±5.3 male younger than 54 jr: 24.0±4.3 / 27.6±7.4 older than 54 jr: 18.7±4.1 / 25.1±6.1	 p<0.001 p<0.001 p<0.001 p<0.001
Häkkinnen 2002♠ MB	23 (100%) ERA LRA	12 (100%) area residence	Hospital	ERA: 41 (9) LRA: 49 (7)	ERA: 165 (9) cm 61 (13) kg fat: 30.4 (6.6) % LRA: 164 (7) cm 65 (13) kg fat: 34.3 (7.3) %	ERA: 2.9 (0.6) LRA: 14.5 (4.5)	FCI, II	ERA: 26.7±6.8 / LRA: 23.1±6.1 / controls: 24.8±2.3	NS
Kurtais 2006♥ MT	19 (100%)	15 (100%) ?	Rehabilitation centre	48.3 (8.4)	?	128.8 (85.6) months	FCI, II	23.7±4.9 / 26.6±6.0	NS
Rall 1996♦ MB	8 (62.5%)	exercise young : 8 (62.5%) old: 8 (62.5%) control old: 6 (66.7%)	Rheumatology clinic	RA: 41.8±12.6 exercise young : 25.8±2.5 old : 70.3±5.0 control old 68.8±2.9	65.9 (15.9) kg BMI: 25.0 (4.3)	14.6 (12.5)	FC: 2.2 (0.8)	22.9±4.2 / young exercise group: 40.2±10.3 old exercise group: 20.7±5.0 old no exercise group: 21.7±5.7 young exercise versus other groups	 p<0.001

Age, body composition, disease duration are expressed as mean (standard deviation) if not expressed otherwise, VO2max is expressed as mean ± standard deviation. Age and disease duration are expressed in years. n: number of participants with RA or in reference population, MB: maximal bicycle test, MT: maximal treadmill test, SMB: sub-maximal bicycle test, %F: percentage females, FC: Functional Class, GP: general population, BMI: body mass index, RA: rheumatoid arthritis, ERA: early RA, LRA: late RA, ml/kg.min: millilitre per kilogram per minute. Controls matched on ♣: sex, age, body mass index, ♠: age, ♥: age, sex,♦: no information on matching

Aerobic capacity and physical activity, predictors of fatigue in patients with rheumatoid arthritis? A cross-sectional study

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Samenvatting

Doel. Onderzoeken of aerobe capaciteit en fysieke activiteiten gecorreleerd zijn met vermoeidheid bij patiënten met reumatoïde artritis, wanneer gecorrigeerd wordt voor leeftijd, geslacht, pijn en depressie.

Methode. Vermoeidheid (Multi Assessment of Fatigue scale), ziekteactiviteit (Disease Activity Scale 28), pijn, fysiek functioneren en psychologische status (Arthritis Measurement Impact Scale 2), depressie en angst (Hospital Anxiety and Depression Scale), aerobe capaciteit en fysieke activiteit (Short Questionnaire to Asses Health enhancing physical activity) werden gemeten bij 35 individuen. Om de variantie in vermoeidheid verklaard door aerobe capaciteit en fysieke activiteit te meten, werd een hierarchische multiple regressie uitgevoerd.

Resultaten. De gemiddelde (SD) leeftijd van deelnemers was 51.6 (11.2) jaar en 71.4% waren vrouwen. De ziekteduur was 7 (0-27) jaar en de gemiddelde ziekteactiviteit score was 3.7 (1.6). De gemiddelde Global Fatigue Index was 18.73 (10.0). De score voor fysiek functioneren was 1.7 (1.1), voor de Psychological status 3.2 (1.6). Pijn score was 4.1 (2.4) en de mediane score voor depressie was 2,0 (range 0-15). De totale hoeveelheid fysieke activiteit (PA) was 136.9 (72.4) METuur / week en de VO_2max was 27.7 (3.8) ml/kg/min. De variantie van vermoeidheid, verklaard door het model was 45% ($p = 0.08$). Aerobe capaciteit en PA droegen hier 1.1% aan bij. De enige statistisch significante bijdrage werd veroorzaakt door depressive: beta waarde 0.707 ($p < 0,001$).

Conclusie. Er werd geen relatie gevonden tussen de aerobe capaciteit, fysieke activiteit en vermoeidheid. De veronderstelling dat het verbeteren van de aerobe capaciteit tot afname van vermoeidheid leid, lijkt voorbarig. Toekomstig onderzoek zou zich moeten richten op de effectiviteit van interventies die gericht zijn op het veranderen van depressie bij patiënten met reumatoide artritis.

Abstract

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

Method. Fatigue (Multi Assessment of Fatigue scale), disease activity (Disease Activity Scale 28), pain, physical function and psychological status (Arthritis Measurement Impact Scale 2), depression and anxiety (Hospital Anxiety and Depression Scale), aerobic capacity and physical activity (Short Questionnaire to Asses Health enhancing physical activity) were measured in 35 individuals. A hierarchical multiple regression was performed exploring variance of fatigue explained by aerobic capacity and physical activity.

Results. Mean (SD) age of participants was 51.6 (11.2) years and 71.4% were women. Disease duration was 7 (0-27) years and mean disease activity score was 3.7 (1.6).

Mean Global Fatigue Index was 18.73 (10.0). Physical function was 1.7 (1.1) and Psychological status 3.2 (1.6). Pain score was 4.1 (2.4) and median depression score was 2,0 (range 0-15). Total amount of physical activity (PA) was 136.9 (72.4) METhours / week and VO_2max was 27.7 (3.8) ml/kg/min. Total variance of fatigue explained by the model was 45% ($p = 0.08$). Aerobic capacity and PA added 1.1% of explained variance in fatigue. Only depression added a statistically significant contribution: beta value 0.707 ($p < 0,001$).

Conclusion. No relationship was found between aerobic capacity, physical activity and fatigue. The assumption that increasing aerobic capacity leads to lower levels of fatigue seems inaccurate. Future research should explore effectiveness of interventions changing depressive symptoms in persons with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by polyarthritis and erosive synovitis and is associated with progressive impairments and activity limitations.[1, 2] The prevalence in the Dutch adult population is approximately 1% and women have a three times 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 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 do not only experience more frequent, but also, higher levels of fatigue compared to the general population[3].

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 physical activities 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[8], resulting in (premature) fatigue. Although it is generally assumed that physical activity and aerobic capacity are decreased in patients with RA, there is little evidence available to support this assumption[1].

Information on patients' actual level of PA is incomplete and results of studies are not comparable, due to differences in the assessment of PA[1]. The few studies[9-12] that compared aerobic capacity of patients with RA and healthy controls detected no differences in aerobic capacity. Both patients and controls demonstrated a decreased aerobic capacity. This may reflect the fact that half the general population[13, 14] is inactive. It remains unclear if inactivity and decreased aerobic capacity are correlated with higher levels of fatigue experienced by patients with RA compared to healthy controls. Improving aerobic capacity may have a positive influence on fatigue[3]. Several studies show a positive effect of exercise programs on fatigue[15-17]. It is unclear whether this positive effect is the result of increased aerobic capacity through exercise or caused by improving mood and psychosocial well-being[7, 15, 18] and relates to changes in depressive symptoms[19].

Depressive symptoms are experienced by 15% - 23% of patients with RA[20] and correlate with pain and work status. Symptoms related to depression may express

themselves as symptoms related to arthritis. These symptoms include fatigue, difficulty in performing everyday activities and sleep disturbances.
Authors agree on pain and depression being important predictors of fatigue in patients with RA[3, 7, 18, 21-24]. Persons with RA rate fatigue as an important symptom interfering with their quality of life[25]. 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.
The purpose of this study was to explore whether aerobic capacity and physical activity 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 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[26] and were 18 – 65 years of age. Participants were excluded if they had other rheumatic diseases, a history of lower extremity joint replacement operations or a cardiovascular disease. Participants with high cardiovascular risk according to the 'Guidelines for Exercise Testing and Prescription' of the American College of Sports Medicine (ACSM)[27] were also excluded.

Recruitment of participants
Potential participants were invited by the rheumatologist 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[27] were excluded by the nurse.
After signing an informed consent participants were asked to fill out 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

physical therapist with expertise in patients with RA performed all the exercise tests. Patients were recruited during April, May and June 2009. The study was approved by the local Medical Ethics Committee of Martini Hospital.

Measurement instruments

Demographic and disease related variables

The Arthritis Impact Measurement Scales (AIMS2) was used to obtain demographic variables (age, gender, employment) and disease related variables (disease duration, physical function and psychological status)[28]. Disease activity was measured with the Disease Activity Score-28 (DAS28)[29].

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[28]. The Internal consistency coefficients for the health status categories ranges from 0.66 and 0.89[28].

The DAS-28 combines single measures into an overall, continuous measure of rheumatoid arthritis disease activity (28 tender joint count, 28 swollen joint count, erythrocyte sedimentation rate, and a general health assessment on a visual analogue scale). The range of the DAS28 is 0 – 9.4. The level of RA disease activity can be interpreted as low (DAS28 ≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1), or as high disease activity (DAS28 > 5.1)[29]. The DAS28 has good validity, it correlates well with the original DAS ($r > 0.94$) and test-retest reliability is good ($r = 0.8$)[29].

Dependent variable / outcome

Fatigue was assessed by the Multidimensional Assessment of Fatigue scale (MAF), which was developed to measure self-reported fatigue in adults with RA[21]. 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 to POMS fatigue subscale (r = 0.84) and good internal consistency (inter-item correlations 0.53 – 0.83, Cronbach's alpha 0.91 – 0.96)[30].

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[31]. 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 – 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[31]. The HADS has good construct validity. Internal consistency is good, Cronbach's alpha ranges from 0.78 - 0.93 for HADS-A and from 0.82 - 0.90 for HADS-D.

Pain was assessed using the 'Arthritis pain' component of the AIMS2[28]. The Arthritis pain component consists of one question to assess pain intensity and four 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.[32] for use with healthy adults. Minor et al.[33] assessed validity and reliability of this method to estimate aerobic capacity in women with RA. Criterion validity is good, correlation with subjective maximal tests ranges from r = 0.77 to r = 0.80. Test-retest reliability is good, intraclass correlation coefficient ICC = 0.97 (95% CI 0.94 – 0.99).

Following standardized instructions, participants walked on a treadmill (CompactGaitTM, Biometrics BV Netherlands) at a self-selected walking speed between 3.2 and 7.2 km/h at 0% grade. 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 minutes. Heart rate was measured continuously during the test using a handheld pulse oximeter (NPB-40, Nellcor Puritan Bennett LLC.). Final heart rate and selected walking speed were entered into a previously developed equation[32]

to estimate aerobic capacity: VO_2max = 15.1 + 21.8*speed(mph) – 0.327*HR(bpm) – 0.26*speed*age(yrs) + 0.00504*HR*age + 5.98*gender(0 = female; 1 = male).
Physical activity level was assessed with the Short Questionnaire to Asses Health enhancing physical activity (SQUASH)[34]. The SQUASH assesses four 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 (hours/day). Intensity of activities was expressed in metabolic equivalent tasks (MET), using Ainsworths' compendium of physical activities[35]. Total amount of PA was calculated as the sum of time*intensity per activity (METhours per week). The SQUASH is a fairly reliable (r = 0.58) and reasonably valid (r = 0.45) questionnaire[34].

Statistical analysis

The distributions of all variables were examined for normality. Means and SDs were calculated for all normally distributed continuous variables, and medians and interquartile ranges were calculated for continuous variables that were not normally distributed.
Hierarchical multiple regression analysis was performed to examine the unique role of PA and aerobic capacity in explaining variance in fatigue. A hierarchical multiple regression analysis was performed in three steps, to control for age, gender, pain and depressive symptoms. Age and gender were entered in the first step, pain and depressive symptoms were entered in the second step followed by PA and aerobic capacity in the final step. Statistical significance level was set at $p \leq 0.05$. The sample size of this study was set at 60 participants based on the number of independent variables (age, gender, pain, depression, aerobic capacity and PA level) times ten, as recommended for multiple regression analysis by Dawson-Saunders and Trapp[36]. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 14.0 for Windows, SPSS Inc., Chicago, USA).

Results

Twenty-four women and ten men with RA participated in this study. Participant characteristics are presented in Table 1. Mean (SD) age of participants was 51.6 (11.2) years and 35.3 % was employed.

Table 1. characteristics of study participants (n = 34)	
Age, years	51.6 (11.2)
Women, %	70.6
Employed, %	35.3
Disease duration, years	7 (0-27)
Physical function[a]	1.7 (1.1)
Psychological status[b]	3.2 (1.6)
Disease activity[c]	3.7 (1.6)
GFI[d]	18.7 (10.0)
Pain[e]	4.1 (2.4)
HADSD[f]	2.0 (0-15)
HADSA[g]	3.5 (0-16)
VO_2max, ml/kg/min	27.7 (3.8)
PA level, METhours/week	136.9 (72.4)

Variables expressed as mean ± standard deviation if not expressed otherwise
Possible ranges: a. 0-10, higher is more disability. b. 0-10, higher is worse health status. c. 0-9.4, higher is more disease activity. d. 0-50, higher is more fatigue. e. 0-10, higher is more pain. f. 0-21, higher is more depressed. g. 0-21, higher is more anxious.
GFI: Global Fatigue Index. HADSD/HADSA: Hospital Anxiety and Depression Scale. PA: physical activity

Disease duration ranged from 0 – 27 years and mean disease activity score was 3.7 (1.6), which can be interpreted as moderate disease activity.

Participants reported a Physical function of 1.7 (1.1) and a Psychological status of 3.2 (1.6). Arthritis pain mean score was 4.1 (2.4) and participants reported a median 2.0 on HADS depressive symptoms. Total amount of physical activity in one week was 136.9 (72.4) METhours / week and male participants were more active than female participants: 192.6 (76.4) METhours / week versus 113.7 (57.6) METhours / week ($p = 0.02$). All participants performed the submaximal treadmill test and mean VO_2max was 27.7 (3.8) ml/kg/min.

Results were significantly higher for male participants, 31.5 (2.6) ml/kg/min versus 26.2 (2.9) ml/kg/min ($p < 0.001$). Mean Global Fatigue Index was 18.73 (10.0) and in 73.5% of participants intensity of fatigue was unchanged during the course of a week. During some, but not all days of the week 50% of participants experienced fatigue, 11.8% experienced fatigue most of the time. 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 0.299 to -0.648 . It was assumed that the variables were independent of one another (Table 2).

Table 2. intercorrelations of independant variables and GFI

	1	2	3	4	5	6	7
1 Gender	1	-.200	-.108	-.024	-.648*	-.503*	.066
2 Age		1	.299*	.114	-.009	.039	-.085
3 Pain		.	1	.309*	-.218	-.278	.004
4 HADSD				1	-.056	-.256	.622*
5 VO_2max					1	. 389*	-.079
6 PA level						1	-.097
7 GFI							1

HADSD: Hospital Anxiety and Depression Scale (subscale depression), PA: physical activity, GFI: Global Fatigue Index
*: Statistical significance: $p \leq 0.05$

Age and gender and depressive symptoms and pain were entered in the first step and second step of the regression analysis. Age and gender made no significant contribution. After entry of aerobic capacity and PA in the third step the total variance explained by the model was 45% ($p = 0.08$). Aerobic capacity and PA added 1.1% of explained variance in fatigue. In this model only depressive symptoms added a unique statistically significant contribution, with a beta value of 0.707 ($p< 0.001$). Results are presented in Table 3.

Table 3. Hierarchical multiple regression analysis with the dependant variable Global Fatigue Index

Step	Group	R^2	p-value	Beta	p-value
1	Age	.010	.860	-.114	.463
	Gender			.021	.927
2	Pain	.439	.002	- .175	.329
	Depression			.707	.000
3	Aerobic capacity	.450	.008	-.100	.629
	Physical activity			.089	.632

Statistical significance level: $p \leq 0.05$

Discussion

The purpose of this study was to explore whether aerobic capacity and physical activity 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 a whole the model explained 45% of the variance of fatigue. Depressive symptoms was the only variable with a unique statistically significant contribution.

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 an fatigue[37]. 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[32, 33]. To determine level of PA METhours / week were used. The only study using the SQUASH[14] to determine PA level in patients with RA, measured PA in minutes / week. Compared to those results the patients in the present study were younger (51.4 – 60.5 years) and more active (2507 - 1535 minutes / week). Results from the present study do not seem to support the idea that patients with RA are fatigued due to deconditioning.

It is possible that the effect of aerobic exercises on fatigue is a result of the positive influence aerobic exercise has on depressive symptoms[19]. In the present study depressive symptoms were highly correlated with fatigue, this is even more interesting since patients experienced mild depressive symptoms. Only two persons reached the lower cut-off point for a possible case (8 points) and one person was considered a probable case (> 11 points). 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. Pollard et al.[38] found a strong correlation between fatigue and depression, other comorbidities such as cardiovascular and respiratory diseases were not correlated to fatigue. Depressive symptoms may express themselves as the inability to perform activities. The results show an almost significant bivariate correlation between depressive symptoms and PA level: -0.302 ($p = 0.053$). These findings are in agreement with results from Rupp et al.[3] who detected a moderate correlation of depression with reduced activity. In a study on depressive history and RA fatigue, Jump et al.[39] found that fatigue was negatively associated with self

efficacy. Persons with a history of depression experienced lower levels of self efficacy to complete daily activities. Decreased daily activities associated with fatigue might be a result of depressive symptoms or self efficacy instead of the result of deconditioning. In earlier research self efficacy is described as being an important factor predicting higher levels of PA[40].

In this study pain did not significantly contribute to the variance of fatigue. This finding seems in contrast with results from studies of Belza et al.[21] and Huyser et al.[6, 21] In both studies level of pain was positively correlated to fatigue and explained 19% of the variance of fatigue. It is difficult to compare results because of differences in the statistical analysis. Belza used hierarchical multiple regression and entered pain in one step of the analysis and depression in the next. Huyser used a composite score of multiple pain measurement scales. In the present study depressive symptoms and pain were simultaneously entered in the regression analysis. Depression in patients with RA is linked to joint pain[39], in the present study a correlation of 0.393 ($p = 0.013$) existed. This may have influenced the results of the multivariate analysis.

The fact that gender was not significantly associated with fatigue confirms earlier inconsistent findings. In the study of Reimsma et al.[18] and Wolfe et al.[24] gender was not a significant factor, while Belza et al.[21] 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 endpoints, such as housework, should produce more fatigue symptoms. Compared to the present study in the study of Belza et al. a higher percentage of the participants was female (75% - 69,2%) and fatigue particularly affected doing household activities. In the present study household activities was not the most affected and mean GFI did not differ significantly between men and women (17,7 – 18,6; $p = 0,83$).

Patients in the present study were younger and experienced less pain and disability than patients in comparable studies[18, 28, 41]. Disease duration was relatively short and disease activity moderate. Lee et al.[37] found that patients exercising regularly experienced less pain compared to non-exercisers. Global Fatigue Index in exercisers was higher than in participants of the present study (24.3 – 18.1). In an other study[17] exploring the effect of aerobic exercise participants had a GFI of 18.6 and a VO_2max of 22.7 ml/kg/min. In the present study GFI was comparable but participants had a higher VO_2max: 28.1 ml/kg/min. Of only six patients VO_2max was

below normative age and gender related average VO_2max. It is possible this has influenced results.

This study has several limitations. First, due to limitations on the recruitment period we were not able to include 60 participants, recommended for multiple regression analysis with six independent variables. Second, disease severity and characteristics of participants may differ from other populations, although results were comparable to results of a ten year follow up study of patients with RA that suggests health status is improving[41]. Generalisability may be compromised. Third, due to the cross-sectional nature of the study the way depression, PA level and fatigue relate to each other 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 way these variables interact. Fourth, the Multi Assessment of Fatigue scale is developed to explore four 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 to complex scales[38] and are easier to use. If we want a more complete picture of fatigue and the relationships with RA, validation research on the use of the single domains of the MAF needs to be done.

Conclusion

No relationship was found between aerobic capacity, level of PA and fatigue. This study confirms earlier results that depression is a predictor of fatigue. Depression may result in decreased daily activities and fatigue. A 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 effectiveness of interventions changing depressive symptoms in persons with RA and the relation with level of PA and fatigue.

Reference List

(1) Plasqui G. The role of physical activity in rheumatoid arthritis. Physiol Behav 2008 May 23;94(2):270-5.
(2) van der Heijde D. Impact of rheumatoid arthritis on physical function during the first five years. No longer a question mark? Rheumatology (UK) 2000;39(6):579-80.
(3) Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. Arthritis Rheum 2004 August 15;51(4):578-85.
(4) Belza B. The impact of fatigue on exercise performance. Arthritis Care Res 1994 December;7(4):176-80.
(5) Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res 2004 February;56(2):157-70.
(6) Huyser BA, Parker JC, Thoreson R, Smarr KL, Johnson JC, Hoffman R. Predictors of subjective fatigue among individuals with rheumatoid arthritis. Arthritis Rheum 1998 December;41(12):2230-7.
(7) Repping-Wuts H, Fransen J, van AT, Bleijenberg G, van RP. Persistent severe fatigue in patients with rheumatoid arthritis. J Clin Nurs 2007 November;16(11C):377-83.
(8) Evans WJ, Lambert CP. Physiological basis of fatigue. Am J Phys Med Rehabil 2007 January;86(1 Suppl):S29-S46.
(9) de Carvalho MR, Tebexreni AS, Salles CA, Barros NT, Natour J. Oxygen uptake during walking in patients with rheumatoid arthritis--a controlled study. J Rheumatol 2004 April;31(4):655-62.
(10) Hakkinen A, Haanonan P, Nyman K, Hakkinen K. Aerobic and neuromuscular performance capacity of physically active females with early or long-term rheumatoid arthritis compared to matched healthy women. Scand J Rheumatol 2002;31(6):345-50.
(11) Kurtais Y, Tur BS, Elhan AH, Erdogan MF, Yalcin P. Hypothalamic-pituitary-adrenal hormonal responses to exercise stress test in patients with rheumatoid arthritis compared to healthy controls. J Rheumatol 2006 August;33(8):1530-7.
(12) Rall LC, Meydani SN, Kehayias JJ, wson-Hughes B, Roubenoff R. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheum 1996 March;39(3):415-26.
(13) Mancuso CA, Rincon M, Sayles W, Paget SA. Comparison of energy expenditure from lifestyle physical activities between patients with rheumatoid arthritis and healthy controls. Arthritis Rheum 2007 May 15;57(4):672-8.
(14) van den Berg MH, de B, I, le CS, Breedveld FC, Vliet Vlieland TP. Are patients with rheumatoid arthritis less physically active than the general population? J Clin Rheumatol 2007 August;13(4):181-6.
(15) Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review. J Adv Nurs 2006 December;56(6):617-35.

(16) Neuberger GB, Press AN, Lindsley HB et al. Effects of exercise on fatigue, aerobic fitness, and disease activity measures in persons with rheumatoid arthritis. Res Nurs Health 1997 June;20(3):195-204.
(17) Neuberger GB, Aaronson LS, Gajewski B et al. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. Arthritis Rheum 2007 August 15;57(6):943-52.
(18) Riemsma RP, Rasker JJ, Taal E, Griep EN, Wouters JM, Wiegman O. Fatigue in rheumatoid arthritis: the role of self-efficacy and problematic social support. Br J Rheumatol 1998 October;37(10):1042-6.
(19) Mayoux-Benhamou A, Giraudet-Le Quintrec JS, Ravaud P et al. Influence of patient education on exercise compliance in rheumatoid arthritis: a prospective 12-month randomized controlled trial. J Rheumatol 2008 February;35(2):216-23.
(20) Pincus T, Griffith J, Pearce S, Isenberg D. Prevalence of self-reported depression in patients with rheumatoid arthritis. Br J Rheumatol 1996 September;35(9):879-83.
(21) Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993 March;42(2):93-9.
(22) Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol 1995 April;22(4):639-43.
(23) Mancuso CA, Rincon M, Sayles W, Paget SA. Psychosocial variables and fatigue: a longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. J Rheumatol 2006 August;33(8):1496-502.
(24) Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. J Rheumatol 2004 November;31(11):2115-20.
(25) Repping-Wuts H, Uitterhoeve R, van RP, van AT. Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study. Int J Nurs Stud 2008 July;45(7):995-1002.
(26) Arnett FC, Hunder GG, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheum 1988;Vol. 31(no. 3):315-24.
(27) Hagberg JM. Exercise assessment of arthritic and elderly individuals. Baillieres Clin Rheumatol 1994 February;8(1):29-52.
(28) Riemsma RP, Taal E, Rasker JJ, Houtman PM, Van Paassen HC, Wiegman O. Evaluation of a Dutch version of the AIMS2 for patients with rheumatoid arthritis. Br J Rheumatol 1996 August;35(8):755-60.
(29) Fransen J, Stucki G, van Riel PL. Rheumatoid Arthritis Measures; Disease Activity Score (DAS), Disease Activity Score-28 (DAS28), Rapid Assessment of Disease Activity in Rheumatology (RADAR), and Rheumatoid Arthritis Disease Activity Index (RADAI). Arthritis & Rheum 2003;Vol 49(No 5S):S214-S224.
(30) Neuberger GB. Measures of Fatigue; The Fatigue Questionnaire, Fatigue Severity Scale, Multidimensional Assessment of Fatigue Scale, and Short Form-36 Vitality (Energy/Fatigue) Subscale of the Short Form Health Survey . Arthritis & Rheum 2003;49(5S):S175-S183.
(31) Karen L.Smarr. Measures of Depression and Depressive Symptoms; The Beck Depression Inventory (BDI), Center for Epidemiological Studies-Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital

Anxiety and Depression Scale (HADS), and Primary Care Evaluation of Mental Disorders-Mood Module (PRIME-MD) . Arthritis & Rheumatism (Arthritis Care & Research) 2003 October 15;Vol. 49(No. 5S):134-46.
(32) Ebbeling CB, Ward A, Puleo EM, Widrick J, Rippe JM. Development of a single-stage submaximal treadmill walking test. Med Sci Sports Exerc 1991 August;23(8):966-73.
(33) Minor MA, Johnson JC. Reliability and validity of a submaximal treadmill test to estimate aerobic capacity in women with rheumatic disease. J Rheumatol 1996 September;23(9):1517-23.
(34) Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol 2003 December;56(12):1163-9.
(35) Ainsworth BE, Haskell WL, Whitt MC et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000 September;32(9 Suppl):S498-S504.
(36) Dawson-Saunders B, Trapp RG. Basic and Clinical Biostatics. Norwalk: Appleton & Lange; 1998.
(37) Lee EO, Kim JI, Davis AH, Kim I. Effects of regular exercise on pain, fatigue, and disability in patients with rheumatoid arthritis. Fam Community Health 2006 October;29(4):320-7.
(38) Pollard LC, Choy EH, Gonzalez J, Khoshaba B, Scott DL. Fatigue in rheumatoid arthritis reflects pain, not disease activity. Rheumatology (Oxford) 2006 July;45(7):885-9.
(39) Jump RL, Fifield J, Tennen H, Reisine S, Giuliano AJ. History of affective disorder and the experience of fatigue in rheumatoid arthritis. Arthritis Rheum 2004 April 15;51(2):239-45.
(40) Greene BL, Haldeman GF, Kaminski A, Neal K, Lim SS, Conn DL. Factors affecting physical activity behavior in urban adults with arthritis who are predominantly African-American and female. Phys Ther 2006 April;86(4):510-9.
(41) Uhlig T, Heiberg T, Mowinckel P, Kvien TK. Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004. Ann Rheum Dis 2008 December;67(12):1710-5.

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