Cardiovascular training improves fitness in patients with ankylosing spondylitis.

Karin Niedermann, PhD [1,2], Eduard Sidelnikov, PhD[3], Claudia Muggli[4], Hanne Dagfinrud, PhD[5], Matthias Hermann, MD[6,7], Giorgio Tamborrini, MD[2], Adrian Ciurea, MD[2]*, Heike Bischoff-Ferrari, PhD[2,3]*

AC and HBF contributed equally to this study

[1]Zurich University of Applied Sciences, School of Health Professions, Institute of Physiotherapy, Winterthur, Switzerland

[2]Department of Rheumatology (RUZ), University Hospital Zurich, Switzerland

[3]Center on Aging and Mobility, University of Zurich and City Hospital Waid, Switzerland

[4]Swiss Ankylosing Spondylitis Association, Zurich, Switzerland

[5]Section for Health Science, University of Oslo, Norway

[6]Department of Cardiology, University Hospital Zurich

[7]Zurich Rehabilitation Clinic Wald, Cardiology Rehabilitation Wald

Corresponding author

Karin Niedermann, PhD, MPH, PT

Institute of Physiotherapy

Zurich University of Applied Sciences, School of Health Professions

Technikumstr. 71

8401 Winterthur

Switzerland

Tel +41 58 934 63 46   Fax +41 58 935 63 46

Email karin.niedermann@zhaw.ch

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ABSTRACT

Objective: Several studies suggest that patients with ankylosing spondylitis (AS) have an increased risk of cardiovascular disease. This study aimed to evaluate the effects of a 12-week individually heart rate-monitored, moderately intensive cardiovascular training on cardiovascular fitness and perceived disease activity in AS patients.

Methods: Patients diagnosed with AS according to modified New York criteria were randomised to either 'cardiovascular training' or 'attention control'. The training group performed three cardiovascular trainings per week. All participants attended one weekly usual care flexibility training. Attention control contained regular discussion groups on coping strategies. Adherence was self-monitored. Assessments were performed at baseline and after the intervention period of 3 months. Physical fitness was the primary endpoint, measured in watts using a submaximal bicycle test following the PWC75% protocol. All analyses controlled for gender, age, body mass index, baseline fitness and physical activity levels, and BASDAI.

Results: Of 106 AS patients enrolled, 40% were women, mean age was 49 (SD +/-12) years. 76.5% of the training group reported exercising at least three times a week. At 3 month follow-up, fitness level in the training group was significantly higher than in the control group (90.32 (SD 4.52) vs.109.84 (SD 4.72) respectively, p=0.001), independent of other covariates. Average BASDAI total score was 0.31 points lower (p = 0.31) in the training group, reaching significance for the 'peripheral pain' subscore (1.19; p=0.01), but not for 'back pain' or 'fatigue'.

Conclusions: Cardiovascular training, in addition to flexibility exercise, increased fitness in AS patients and reduced their peripheral pain.

Significance and Innovations

- AS patients carry an increased risk of cardiovascular disease. This is the first large trial with AS patients focusing on increased cardiovascular fitness.

- Many exercise studies do not achieve sufficient therapeutic validity. This study achieved sufficient therapeutic dose, including sufficient adherence of the patients to the training programme (and the study protocol).

- AS patients are able to perform intensive cardiovascular training without increasing disease activity.

- This study provides basis for studying long-term effects of CV training on further parameters, e.g. biomarkers.

Ankylosing Spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the spine and iliosacral joints and is also associated with extraspinal manifestations, such as peripheral arthritis, enthesitis, uveitis or bowel inflammation (1). The ASAS/EULAR recommendations for the management of AS recommend drug therapy, such as non-steroidal anti-inflammatory drugs (NSAIDs) and, in severe cases, TNF-alpha inhibitors, in combination with spinal flexibility exercise (2). Supervised flexibility exercises in AS patients have been shown to be effective in improving spinal flexibility, physical function, and patients' well-being (3).

Several observational studies suggest that AS patients carry an increased risk of cardiovascular disease (4-7). In addition to chronic inflammation, reduced physical activity due to disease activity, pain and fatigue may further contribute to AS-related cardiovascular disease (7, 8). Regarding physical activity, however, exercise recommendations in AS-guidelines focus on spine flexibility rather than cardiovascular training (2). It can be assumed that these recommendations are widely followed in AS exercise groups, meaning that cardiovascular training is not an established element in AS specific exercise.

A secondary analysis based on the third Cochrane review updated in 2008 included 12 randomised controlled trials on exercise interventions in AS patients (ten from the 2008 Cochrane review and two more recently published ones) and evaluated if the exercise programmes in trials for AS patients were intensive enough to be effective (9). This was determined according to the recommendations of the American College of Sports Medicine (ACSM), which summarize the current evidence for effective exercise interventions (10, 11). Exercise interventions are effective, if they achieve a physiological response, such as increased flexibility, muscular

strength and cardiovascular fitness, which is determined by the frequency, intensity and duration of corresponding exercises, as well as patients' adherence (12). The secondary analysis could not determine conclusively the benefit of cardio-vascular training as all exercise programmes focused on flexibility training, while cardio-vascular fitness components were part of only five exercise programmes, with only one meeting the ACSM recommendations for cardiovascular training.

In order to better define the role of cardiovascular training in AS patients we planned this study to test whether a training designed to improve cardio-vascular fitness is successful in AS patients attending standard flexibility exercise classes. We chose Nordic Walking (NW) as a simple cardio-vascular exercise mode that may attract also inactive individuals. Further, we assumed that NW would be especially suitable for AS patients because of its controlled loading on joints and spine and the enhanced spinal rotation supported by the use of the walking sticks (12, 13).

Patients and Methods

Study design

This randomised controlled trial was conducted at the Department of Rheumatology and the Centre on Aging and Mobility at the University Hospital of Zurich, in close collaboration with the AS patient organisation, the Swiss Ankylosing Spondylitis Association (SVMB, Schweizerische Vereinigung Morbus Bechterew). In addition, we involved a SVMB member in the planning and conduct of the study, ensuring that the trial addressed patient-relevant outcomes and that all the trial documents are understood by the target population and helping recruiting patients.

The Local Ethics Committees approved the study and all participants gave written informed consent. The study has been registered at the International Clinical Trials Registry (identifier NCT00913302).

Participants

Participants diagnosed with AS based on the modified New York criteria (14) were recruited from the SVMB membership registry, including approximately 2500 members and from rheumatology outpatient clinics and private practice rheumatologists in German-speaking regions of Switzerland. Additional inclusion criteria were age >18 years and sufficient German language ability skills. Exclusion criteria were moderate to severe heart disease (functional New York Heart Association Class III and IV) and inability to cycle on an ergometer bike. The most important reasons for non-participation were 'no interest' and 'no time'.

Two recruitment and outdoor training periods from January to May and August to October respectively in two subsequent years ensured similar weather conditions for outdoor NW training.

Randomisation and procedures

Participants were randomised to the training group (cardiovascular training and flexibility exercise) or the control group (attention control and flexibility exercise) by sequentially numbered, concealed treatment allocations prepared in advance by an independent statistician. We used a stratified block randomisation procedure (block size 4) (15) with TNF-α inhibitor treatment (Yes/No) as the stratification variable. We stratified for treatment with TNF inhibitors because of their known effect on the secondary outcome

(BASDAI), which may influence the patients' ability to perform a physical training.

In this trial, participants and physiotherapists who instructed the NW programme were aware of the treatment assignment. However, the physiotherapists who performed baseline and follow-up assessments were blinded to the group allocation.

Interventions:

Cardiovascular training

The training group performed a 12-weeks supervised NW training for 30 minutes twice a week on individually monitored moderate heart rate (HR) intensity levels. Moderate HR intensity ranges of 55 – 75% of the HR_{max} were used for participants who reached less than 100 watts and 65 – 85% of HR_{max} were used for participants who reached at least 100 watts in the baseline bicycle test (10, 11). The intensity range was adjusted if an individual passed over the upper limit during at least 20 minutes. Participants with a low fitness status, i.e. having reached less than 100 Watts in the test and not able to perform the training in their individual lower fitness range for sufficient duration of at least 20 minutes, were first asked to keep walking for at least 20 minutes, and if this was achieved, to perform NW within the intensity range. All participants in the training group were provided with the NW equipment and a heart rate monitor. The NW training was performed in small groups of two to six participants and led by instructing physiotherapists. Furthermore, participants in the training group were asked to perform at least one additional unsupervised, but heart rate-monitored cardiovascular

training, NW or other endurance activities, e.g. outdoor or ergometer biking, to achieve at least three training units per week.

All physiotherapists who instructed the cardiovascular training previously underwent a standardized 4-hour education session.

Attention control

Instead of the NW training, the control group was offered an 'attention control intervention', consisting of monthly 2.5-hours discussion groups on coping strategies and techniques of mindfulness-based stress reduction, led by a psychologist (16).

Standard flexibility exercise

All study participants received the current standard of care and attended a weekly one-hour exercise group, supervised by a physiotherapist, with focus of spinal flexibility as offered by the Swiss AS Association throughout Switzerland.

Training locations and adherence support

Every effort was made to offer a training location closest to the home or work of the participants, and dates and times of group trainings most convenient for them, to facilitate participation. One of the two weekly supervised NW trainings could be attended on the same evening as the flexibility exercise class to reduce time constraints for the participants. All participants received an individual schedule and were asked to keep an adherence diary of all their supervised and unsupervised physical activities.

Assessments

The primary outcome in this trial was *cardiovascular fitness*, assessed with a submaximal bicycle test following the Physical Work Capacity PWC75% protocol to estimate aerobic capacity ($VO_{2\ max}$) (17). A submaximal endurance test is considered more sensitive to change than a maximal endurance test (18). According to the PWC75 % protocol, heart rates at 55%, 65% and 75% of the estimated age-related maximum heart rate are calculated and the Watts produced at these heart rate levels are measured. Although heart disease (NYHA III and IV) was an exclusion criterion, simultaneous electrocardiograms (ECG) were applied in all participants for safety reasons during exercise testing. The cardiologist reviewed all ECGs and if identifying any abnormality, comparison with the patient's cardiovascular disease history was performed to decide whether the patient had to be excluded.

The secondary outcome was perceived disease activity assessed with the BASDAI (The Bath AS Disease Activity Index) on a 0-10 (none to very severe) numerical rating scale NRS (19). Predefined in our protocol, we assessed both the total BASDAI score and the subscales for spinal pain, peripheral pain and fatigue.

Additional exploratory outcomes were 1) *AS-specific functional health*, assessed with the BASFI (The Bath AS Functional Index) (20), the BASMI (The Bath AS Metrology Index) (21) and patient's global assessment of disease activity, general pain and nocturnal pain, all measured on a 0-10 NRS (22). *2) type, amount and intensity of physical activity (PA)* by use of the OIMQ (Office in Motion Questionnaire) (23) and subsequently assigning METs (metabolic equivalents) to each reported activity (24) and an

accelerometer (Actigraph, Manufacturing Technology Inc. (MTI, Fort Walton Beach, FL). The small waist-mounted device is worn for seven days, including a complete weekend, to calculate a reliable average physical activity per day (25, 26), given as *counts/minute* (=number of accelerations) and as *minutes spent in moderate and vigorous activity*, using the cut points defined by Swartz et al. (27). 3) *psychological status,* using the HADS-D (German version of Hospital Anxiety and Depression Scale), assessing anxiety and depression on two 7-item 0-3 scales, (no to severe problems) (28). 4) *perceived general health* using the EURO-Quol, applying a 0-100 VAS (worst to best health) (29) and 5) *lab data of disease activity* (erythrocyte sedimentation rate ESR and C reactive protein CPR) and *metabolism* (cholesterol and triglycerides). Further we calculated the ASDAS using parameters from BASDAI and CRP (30).

Sample size

We based our sample size calculation on the reported means and standard deviations from a similar exercise trial in patients with rheumatoid arthritis (31). To achieve a minimal clinically meaningful difference of 20% for the primary outcome, 49 patients in each group were needed to achieve 90% power to detect this difference.

Statistical analysis

Statistical analysis was performed on an 'intention-to-treat' basis. ANOVA models were used to compare cardiovascular fitness levels, BASDAI total and sub-scores and the exploratory outcome variables at follow-up. The crude models controlled for TNF-α treatment status as stratification variable

and baseline level of the characteristic. The fully adjusted models additionally controlled for age, sex, BMI, smoking status, and baseline levels for perceived disease activity, physical activity and fitness. The data were analysed using SAS v.9.2 statistical software (©2002 – 2008 by SAS Institute, Inc., Cary NC, USA). All statistical tests were two-sided with significance level set at 0.05.

Results

From a total of 185 AS patients who attended the information meetings about the study, 106 confirmed their participation and met the inclusion criteria. 47 of these were enrolled in the first and 59 in the second year of enrollment (figure 1) {image 1}. Baseline characteristics of the two groups were similar (table 1), formal statistical testing detected no significant differences. Participants had no history of heart disease. No signs of coronary ischemia were observed in the ECGs. The cardiologist identified 3 patients with ECGs suggestive of left ventricular hypertrophy and reviewed these patients' cardiovascular history. No exclusions were performed. Although not assessed systematically, participants seemed to have a low cardiovascular risk: 19 patients were on antihypertensive medication, six of them additionally on aspirin and/or statin.

Based on the physiotherapists' protocols for group adherence and on participants' diary, 74.6% of the training group performed at least three training units per week (mean = 3 trainings/week), i.e. two NW training sessions and one additional unsupervised cardio-vascular training unit, but only 25% of the control group performed three or more trainings per week (mean = 1 training per week) .

In a few patients (n=4) who were quite fit already at the beginning and who exercised in the upper intensity range i.e. 65 – 85% of HR_{max}, , the upper limit was increased to 90% of HR_{max}, during the study period; all less fit participants kept exercising in the lower intensity range during the study period, but at the end all of them achieved the required intensity *and* duration .

Treatment effects

    Primary outcome: At 3 month follow-up, both the minimally and the fully adjusted ANOVA model showed a significant benefit in fitness level (expressed in Watts) in the training group compared to the attention control group. In the minimally adjusted model mean (SE) Watts in the training group were 107.98 (3.98), compared to 87.78 (3.87) in the controls (p=0.0004). In the fully adjusted model mean (SE) Watts in the training group were 109.84 (4.72) compared to 90.32 (4.52) in the control group (p=0.001, 95% CI 9.18-31.24), the difference thus being independent of the covariables (table 2). At baseline, two patients in each group were not able to perform the PWC75% test due to their low fitness. At follow up, no patient in the training group, but six patients in the control group were not able to fulfil the PWC75% test protocol, which we consider related to the training effect. The OIMQ questionnaire and the accelerometer were administered before and shortly after the intervention period, assessing the participants' actual physical activity. It may thus not reflect their amount of physical activity during the intervention period, but rather their usual physical activity. On average this seemed to be the same in both groups after study conclusion, although the NW participants had performed substantial more

Secondary outcome (table 2). There was no difference between the two groups in the BASDAI total score at 3 months follow up. For the subscores, we found a significantly lower level of peripheral pain in the training group 1.32 (0.34) compared to 2.36 (0.33) (p=0.02) in the controls (95% CI −1.89 to -0.18), while the subscores for fatigue and neck-back-hip pain were not different between groups.

Additional exploratory outcomes (table 3). There were no significant differences between the two groups regarding the exploratory endpoints, neither in functional measures nor in biomarkers. With respect to the Bath indices, functional limitations were generally low.

Discussion

To our knowledge, this is the first controlled trial to test the effect of cardiovascular training in addition to standard flexibility exercise in AS patients. The results demonstrate that an appropriately designed and conducted cardiovascular training that meets recommended standards leads to significantly improved cardiovascular fitness in AS patients. NW as a strategy to improve cardiovascular fitness in AS patients was well tolerated by the participants, who, despite having a chronic inflammatory condition, were able to exercise frequently, moderately intensive and over a longer period without increasing their disease activity or pain. This supported high adherence to the intervention, which is key when it comes down to exercise studies. The clear association between exercise participation rates and achieved fitness level increased the credibility of the diary protocols and demonstrated adherence to the study protocol. The fact that resting HR did not decrease to the expected extent in the training group may be due to the relatively short training period. Furthermore, the decrease in HR after a course of exercise training has been described mainly in patients with established coronary heart disease of chronic heart failure (32, 33).

Regular physical activity and aerobic exercise training are related to a reduced risk of coronary events in healthy individuals (34-36) subjects with coronary risk factors (37) and established coronary artery disease (32). Therefore, physical activity and aerobic exercise training are recommended by international guidelines for primary and secondary cardiovascular prevention (38, 39).

We show that cardiovascular training is safe and feasible in AS patients and increases their fitness level, independent of their initial fitness level. Whether this benefit translates into the prevention of cardiovascular disease needs to be tested in a larger longer-term clinical trial. Notably, we measured biomarkers of CV-health

as exploratory endpoints (cholesterol, triglycerides), which did not improve

significantly in the training group over control, possibly also due to the short follow-

up. Unfortunately, HDL and LDL cholesterol has not been analysed separately.

Therefore, we could only speculate about potential changes in HDL/LDL ratio with

an increase of protective HDL levels and an according decrease of LDL levels

after the training course. Our initial assumption was that NW training may also

improve fatigue, assessed by BASDAI. Fatigue is one of the predominant

complaints of AS patients and has been shown to be influenced by physical

activity (40). However, although many NW participants reported to feel more

energy after the training and some cardiovascular training studies in RA showed

positive effects on fatigue, even in rather small samples (41, 42), we could not

demonstrate changes in BASDAI total score or in the fatigue subscore in this

group. Disease activity in our sample was generally low because we recruited

patients already treated according to current standards including the availability of

TNF inhibitors and the majority of our patients didn't classify as 'fatigued' (43),

which may partly explain our results.

Interestingly however, participants in the training group reported a significant

improvement in the 'peripheral pain' subscale over control, which addresses

another important endpoint in patients with AS. Literature for effects on pain in

musculoskeletal diseases by cardiovascular training is scarce, only two early

studies in rheumatoid arthritis (RA) (31, 44), found that the dynamic exercise

groups significantly decreased the number of clinically active joints. The 2006

Cochrane review on dynamic exercise therapy for treating rheumatoid arthritis,

evaluating six trials, however concluded that there were no positive, but also no

negative effects on pain (45).

Our trial had several strengths. First, it was the largest exercise trial in AS patients so far and, in addition to providing an intervention based on the current and established ASCM recommendations, we chose a training strategy that was feasible and well tolerated by participants. Further, we assured high quality outcome assessments by blinding the assessment physiotherapists at baseline and follow-up to the treatment allocation. Also, our study was appropriately powered to detect a statistically significant difference for the primary outcome. Moreover, the attention control intervention lends credibility to the training effect of NW.

There are also limitations to our study. These include a limited sample size for the secondary and exploratory endpoints tested and the short follow-up of 3 months. Further, no efforts were made to support the participants' achieved fitness levels. However support is usually necessary to keep patients on their achieved physical activity levels (46). Physiotherapists' coaching of early-stage RA patients, in terms of two face-to-face meetings and subsequent regular telephone calls, has been shown to successfully support their physical activity adherence over one year (47). However, after another year without any support, no differences in physical activity levels were present compared to the controls (48). It seems that even distance-coaching is effective to keep people active and to maintain exercise effects.

In summary, the improved cardiovascular fitness and the significant improvement in BASDAI peripheral pain support the inclusion of NW as a cardiovascular training strategy in patients with AS. Future research should test the long-term effects of NW on cardio-vascular health in patients with AS.

Acknowledgement

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Table 1: Baseline characteristics of participants

	Training group (n=53)	Control group (n=53)	p
Men, No (proportion)	34 (64%)	34 (64%)	1.00
Age, years, mean (SD)	50.1 (11.9)	47.6 (12.4)	0.29
Disease duration, (years) median (range)	9 (0.5 -45)	8 (0.5 – 39)	0.60
BMI (kg/m^2), mean (SD)	25.2 (4.1)	25.5 (4.3)	0.71
Smokers (proportion)	11 (20%)	16 (30%)	0.37
TNF treatment yes (%)	15 (28%)	16 (30%)	1.00
Fitness (in Watts)	91.3 (37.4)	101.4 (45.5)	0.21
Resting heart rate	82.3 (11.4)	82.1 (13.5)	0.94
Heart rate at end of test	130.5 (9.6)	132.7 (10.3)	0.29
BASDAI (0-10)	3.3 (1.9)	3.6 (2.1)	0.57
BASDAI fatigue (0-10)	4.4 (2.4)	5.0 (2.7)	0.27
BASDAI neck-back-hip pain (0-10)	3.8 (2.5)	4.2 (2.7)	0.65
BASDAI joint pain (0-10)	2.2 (2.3)	2.7 (2.6)	0.36
BASG night pain (0-10)	3.1 (2.8)	2.9 (2.8)	0.59
BASG pain (0-10)	3.2 (2.0)	3.5 (2.5)	0.80
BASG disease activity (0-10)	3.7 (2.3)	4.2 (3.1)	0.72
BASFI (0-10)	2.4 (1.9)	2.4 (2.1)	0.92
BASMI (0-10)	2.9 (2.1)	2.8 (1.9)	0.99
OIMQ (MET per week)	71.8 (39.1)	78.4 (58.5)	0.89
Accelerometer, counts/min), mean (SD) per day	336 3 (184.9)	370.5 (145.0)	0.18

Accelerometer, moderate activity (min/week)	145.9 (54.2)	170.4 (64.5)	0.09
PA (Accelerometer, units of vigorous activity)	11.1 (9.4)	13.6 (12.9)	0.50
HADS Anxiety (0-21)	6.9 (5.3)	6.7 (4.5)	0.92
HADS Depression (0-21)	5.2 (4.4)	5.0 (4.5)	0.70
EURO-Quol Health score (0-100)	64.5 (22.0)	65.9 (21.2)	0.75
$ASDAS_{(CRP)}$	7.5 (9.8)	6.4 (8.7)	0.73
CRP (mg/l)	2.2 (0.8)	2.3 (1.0)	0.40
Cholesterol (mmol/l)	5.4 (0.9)	5.3 (1.0)	0.41
Triglycerides (mmol/l)	1.1 (0.6)	1.4 (1.0)	0.07

Tests used: χ^2 test for categorical variables, nonparametric statistics (Wilcoxon rank-sum test) for all continuous variables.

Values are means and SD, unless stated otherwise.

SD, Standard deviation; BMI, body mass index; TNF, tumor necrosis factor; CRP, C-reactive protein; AS DAS_{CRP}, ankylosing spondylitis disease activity score (calculated with CRP values); BASDAI, Bath AS Disease Activity Index; BASFI = the Bath AS Functional Index; BASMI = Bath AS Metrology Index.

Table 2: Primary and secondary outcomes at 3 months follow up

Primary outcome	Minimally adjusted ANOVA model**			Multivariate adjusted ANOVA model***		
	Exercise Group	**Control Group**	**P value**	**Exercise Group**	**Control Group**	**P value**
Fitness level (Watts)*	107.98 (3.98)	87.78 (3.87)	**0.0004**	109.84 (4.72)	90.32 (4.52)	**0.001**
Secondary outcome						
BASDAI score total (0-10)*	3.07 (0.20)	3.35 (0.20)	0.33	2.84 (0.24)	3.15 (0.23)	0.31
BASDAI score fatigue (0-10)	3.73 (0.32)	4.29 (0.32)	0.22	3.64 (0.39)	4.39 (0.37)	0.13
BASDAI score neck-back-hip pain (0-10)	3.31 (0.33)	4.15 (0.30)	0.07	3.25 (0.38)	3.98 (0.36)	0.13
BASDAI score joint pain (0-10)	2.05 (0.31)	2.74 (0.30)	0.11	1.32 (0.34)	2.36 (0.33)	**0.02**

All values are means and standard deviation (SD), unless stated otherwise

Bold = Significant on 0.001 and 0.05 level respectively

* baseline values given in table 1

** adjusted for TNF alpha treatment (stratification variable) and baseline level of the characteristic

*** adjusted for age, sex, BMI, smoking status, baseline physical activity, baseline perceived disease activity, TNF alpha and baseline

of characteristic

BASDAI = the Bath AS Disease Activity Index

Table 3: Additional exploratory outcomes

Outcome	Minimally adjusted ANOVA model*			Multivariate adjusted ANOVA model**		
	Exercise Group	Control Group	P value	Exercise Group	Control Group	P value
BAS-G night pain (0-10)	3.00 (0.26)	2.63 (0.27)	0.32	2.26 (0.32)	2.64 (0.31)	0.34
BAS-G pain (0-10)	3.25 (0.29)	3.39 (0.28)	0.74	3.13 (0.35)	3.20 (0.33)	0.88
BAS-G disease activity (0-10)	4.05 (0.35)	3.74 (0.34)	0.52	3.87 (0.40)	3.59 (0.38)	0.59
BASFI-score (0-10)*	2.49 (1.77)	2.41 (1.70)	0.73	2.53 (0.21)	2.40 (0.20)	0.63
BASMI score (0-10)*	2.64 (0.25)	3.02 (0.24)	0.27	2.40 (0.28)	2.66 (0.28)	0.46
OIMQ (MET per week)	51.37 (6.27)	55.40 (6.39)	0.65	52.94 (7.24)	58.03 (7.51)	0.61
Accelerometer, counts/min), mean (SD)	333.35 (22.16)	335.34	0.95	373.98 (30.00)	349.87	0.45

per day		(20.44)			(24.95)	
Accelerometer, moderate activity	141.17 (8.55)	147.81 (7.94)	0.57	149.14 (11.58)	146.58 (9.53)	0.83
PA (Accelerometer, units of vigorous activity)	7.45 (1.25)	9.50 (1.32)	0.26	8.74 (1.77)	9.36 (1.52)	0.74
Resting heart rate	81.10 (1.95)	81.57 (1.86)	0.86	77.89 (1.93)	80.27 (1.91)	0.33
Heart rate at end of test	128.30 (0.59)	128.37 (0.59)	0.93	128 92 (0.69)	128.70 (0.68)	0.80
HADS Anxiety (0-21)	6.27 (0.35)	6.58 (0.34)	0.52	6.58 (0.40)	6.63 (0.39)	0.93
HADS Depression (0-21)	5.10 (0.31)	4.48 (0.30)	0.16	5.18 (0.37)	4.33 (0.35)	0.07
EURO-Quol Health score (0-100)	64.24 (3.05)	63.01 (2.93)	0.77	61.97 (3.31)	65.19 (3.13)	0.44
ASDAS$_{(CRP)}$*	2.26 (0.15)	2.16 (0.15)	0.62	2.43 (0.17)	2.23 (0.18)	0.38
CRP (mg/l)*	6.27 (1.08)	4.95 (1.07)	0.39	7.49 (1.22)	4.93 (1.30)	0.12

Cholesterol (mmol/l)*		5.66 (0.15)	5.90 (0.16)	0.28	5.66 (0.18)	5.93 (0.19)	0.24
Triglycerides (mmol/l)*		1.30 (0.12)	1.42 (0.13)	0.48	1.23 (0.14)	1.35 (0.16)	0.52

All values are means and standard deviation (SD), unless stated otherwise.

*Adjusted for TNF alpha and baseline level of the characteristic

** adjusted for age, sex, BMI, smoking status, baseline physical activity, baseline fitness level, BASDAI, TNF alpha treatment and baseline level of the characteristic

BAS-G = Bath AS Patient Global Score; BASFI = the Bath AS Functional Index; BASMI = Bath AS Metrology Index; PA = Physical Activity; OIMQ = Office in Motion Questionnaire; MET, metabolic equivalents; HADS = Hospital Anxiety and Depression Scale; EURO-Quol = quality of life questionnaire; AS DAS$_{CRP}$, ankylosing spondylitis disease activity score (calculated with CRP values); CRP, C-reactive protein;

Figure 1: Trial flow chart