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# High-intensity interval training improves cardiovascular and physical health in patients with rheumatoid arthritis: a multicentre randomised controlled trial

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bjsports-2024-108369).

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Accepted 21 July 2024



**To cite:** Bilberg A, Mannerkorpi K, Borjesson M, *et al*. *Br J Sports Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjsports-2024-108369

## ABSTRACT

**Objectives** Patients with rheumatoid arthritis (RA) have substantially elevated risk for cardiovascular diseases, and low cardiorespiratory fitness ($VO_2$max) is a major mediator. The aim of this assessor-blinded, two-armed multicentre randomised controlled trial was to evaluate the effects of high-intensity interval training (HIIT) and strength exercise on cardiovascular health, physical fitness and overall health in patients with RA.

**Methods** In total, 87 patients (86% female; aged 20–60 years) were randomly assigned to an intervention group (IG) or a control group (CG). The IG performed HIIT and strength exercise for 12 weeks. The CG was instructed to be physically active on a moderately intensive level, ≥150 min/week. Primary outcome was change in $VO_2$max. Secondary outcomes were changes in anthropometry measures, muscle strength, overall health (Visual Analogue Scale (VAS)-Global), Patient Global Impression of Change (PGIC), pain and disease activity (Disease Activity Score in 28 joints (DAS28)).

**Results** There was a significant mean group difference of change on $VO_2$max (3.71 mL/kg/min; 95% CI 2.16, 5.25) in favour of the IG. Significant mean group differences of change were also seen for $O_2$-pulse (1.38; 95% CI 0.85 to 1.91), waist circumference (−2.6; 95% CI −5.09 to −0.18), 1-minute sit-to-stand (5.0; 95% CI 3.35 to 6.72), handgrip strength (28.5; 95% CI 3.80 to 52.8), overall health (−14.7; 95% CI −23.8 to −5.50) and PGIC ($p<0.0001$) in favour of the IG. No significant mean group differences of change were found for pain (−4.0; 95% CI −13.07 to 5.06), DAS28 (−0.25; 95% CI −0.60 to 0.10) and erythrocyte sedimentation rate (−0.64; 95% CI −3.23 to 1.90).

**Conclusion** Supervised HIIT and strength exercise improved cardiovascular health, physical fitness and overall health without a deterioration in pain and disease activity and should be considered in patients with well-controlled RA.

**Trial registration number** NCT05768165.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis (RA) have an elevated risk for cardiovascular diseases compared with the general population.

⇒ Exercise has the potential to improve cardiovascular health in RA, although only a minority of patients engage in exercise on a high enough level to improve cardiorespiratory fitness.

### WHAT THIS STUDY ADDS

⇒ Supervised high-intensity interval training (HIIT) and strength exercise for 12 weeks significantly improved $VO_2$max, waist circumference, muscle strength and overall health without accentuating disease activity and pain in patients with well-controlled RA.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Supervised HIIT and strength exercise appear to be feasible and well tolerated by patients and could be recommended to improve cardiovascular and physical health in patients with well-controlled RA.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic autoimmune disease characterised by systemic inflammation and peripheral arthritis.[1 2] Clinical symptoms, such as pain, stiffness and fatigue, often lead to functional disability[3] and deterioration in health.[4] Patients with RA have an increased prevalence of comorbidities,[5] mainly cardiovascular diseases (CVDs).[6] The elevated CVD risk of RA is comparable to that of type 2 diabetes mellitus.[7] Increased cardiovascular morbidity and mortality in RA have partially been attributed to myocardial infarction and congestive heart failure, caused by atherosclerotic events.[6]

The CVD risk is linked to the systemic inflammatory process in combination with increased levels of traditional risk factors.[8 9] Physical inactivity has been associated with an adverse CVD risk profile,[10] and cardiorespiratory fitness (CRF) is similarly inversely associated with CVD morbidity and mortality in RA.[11] Exercise shows beneficial effects on CRF,[12] disease activity,[13] possibly diminishes other cardiovascular risk factors in RA[14] and is recommended as part of patient standard care.[15] However, time restriction, pain and fatigue are common barriers for exercise in individuals with RA,[16] and only a minority of patients engage in exercise at high enough intensity to improve CRF.[10]

A time-efficient method to improve cardiorespiratory fitness is high-intensity interval training (HIIT), which involves alternating bouts of high

**Table 1** Description of the exercise protocol

| Exercise protocol | |
|---|---|
| The exercise programme followed the American College of Sports Medicine exercise recommendations. Individually tailored according to physical capacity and physical ability. Exercise guidance followed the principles of self-efficacy and motivational support, applying supervision, identification of possible limitations and barriers, an individual exercise diary, and continuous dialogue with individual feedback by the physiotherapist. | |
| High-intensity interval training | |
| Delivery | Supervised by a physiotherapist at the physiotherapeutic facility at a hospital |
| Type | Exercise on a cycle ergometer |
| Frequency | Two times per week |
| Intensity | 10 min warm up at 60–70% of HRmax. 4×4 min interval exercise at 90–95% HRmax with 3 min of active recovery period at 70% HRmax between each interval. 3 min cool down at 60–70% HRmax. The intensity was controlled by a heart rate sensor (Polar H10) connected to an exercise app on the patient's cellphone during each session. The individual HRmax was determined at the end of the CPET at baseline. |
| Progression | The intensity of the cardiorespiratory exercise was gradually increased to the pulse target zone (90–95% HRmax) over the first 2 weeks, depending on the subject's adaptation to the exercise protocol. |
| Time | 38 min |
| Muscle strength exercise | |
| Delivery | Supervised by a physiotherapist at the physiotherapeutic facility at a hospital |
| Type | Exercises of large muscle groups. A total of eight exercises, individually adapted. Examples of exercises: leg press, squat, hip extension, pull down, biceps curl with free weights, rows to chest, sit ups, lumbar back extension |
| Frequency | Two times per week |
| Repetition | 8–10 |
| Sets | 2–3 |
| Progression | Weeks 1–2: 50–60% of 1RM, 15 repetition, 1–2 sets<br>Weeks 3–6: 60–70% of 1RM, 8–10 repetition, 2–3 sets<br>Weeks 7–12: 70–80% of 1RM, 8–10 repetition, 2–3 sets |
| Time | 20 min |
| Non-supervised aerobic exercise | |
| Delivery | Individual exercise of the patient's own choice |
| Type | Walking/running/bicycling, outdoor or at fitness centre |
| Frequency | One day per week |
| Intensity | 70% of HRmax, including 10 min of warm-up on lower intensity, controlled by a heart rate sensor (Polar H10) connected to an exercise app on the patient's cellphone or pulse watch. |
| Time | 40 min |
| **Control group**<br>Individual information of the general recommendations for physical activity, with encouragement to be physically active on moderate intensity ≥150 min/week.<br>**Home exercise**<br>A total of five exercises including muscle strengthening of lower extremities and trunk and one leg standing, without any exercise equipment. | |
| CPET, cardiopulmonary exercise test; HRmax, heart rate maximum; 1RM, one repetition maximum. | |

intensity on 90–95% heart rate maximum (HRmax) and periods of lower intensity.[17] The exercise mode is suggested to result in greater improvements in $VO_2$max than moderately continuous exercise.[18] This is important when aiming to prevent CVD since the risk for CV morbidity and mortality decreases for every increment in 1 mL of $VO_2$max.[19] However, to date, the evidence of HIIT on cardiovascular health in RA is scarce.[20] Cardiorespiratory exercise in combination with muscle strength exercise has been recognised to have the largest potential to reduce CV mortality[21] and to improve health.[22] Hence, the primary aim of this study was to evaluate the effects of HIIT and strength exercise on cardiorespiratory fitness. The secondary aim included changes in muscle strength, anthropometry measures, lipid status, overall health, Patient Global Impression of Change (PGIC), pain and disease activity (Disease Activity Score in 28 joints (DAS28)).

## METHODS

### Design

The study was designed as an assessor-blinded, two-armed multicentre randomised controlled trial comparing the effects of 12-week supervised high-intensity exercise with health-promoting physical activity.

### Participants

Patients with RA were recruited from the rheumatology departments at Sahlgrenska University Hospital and Uddevalla Hospital through the Swedish Rheumatology Quality Register. The recruitment, intervention and data collection were performed between August 2021 and May 2023. Patients fulfilling the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) 1987/2010 criteria for RA,[23 24] with disease duration >1 year, aged 20–60 years, stable treatment on antirheumatic drugs for the past 3 months, and low-to-moderate disease activity (DAS28 <5.1) were eligible for inclusion. DAS28 <5.1 was chosen as upper limit for inclusion for safety considerations. Exclusion criteria were symptoms of CVD, other comorbidities, physical disabilities and pregnancy precluding participation in high-intensity exercise, engagement in regular cardiorespiratory exercise on high intensity level (>1 hour/week for the past 6 months), inability to understand and speak Swedish.

The study complied with the Declaration of Helsinki. Informed written consent was obtained from all patients before baseline examinations. The trial was registered prospectively on 'FoU in Sweden' (Research and Development in Sweden) (registration number: 275642) and retrospectively on ClinicalTrials.gov (NCT 05768165) (online supplemental file 1).

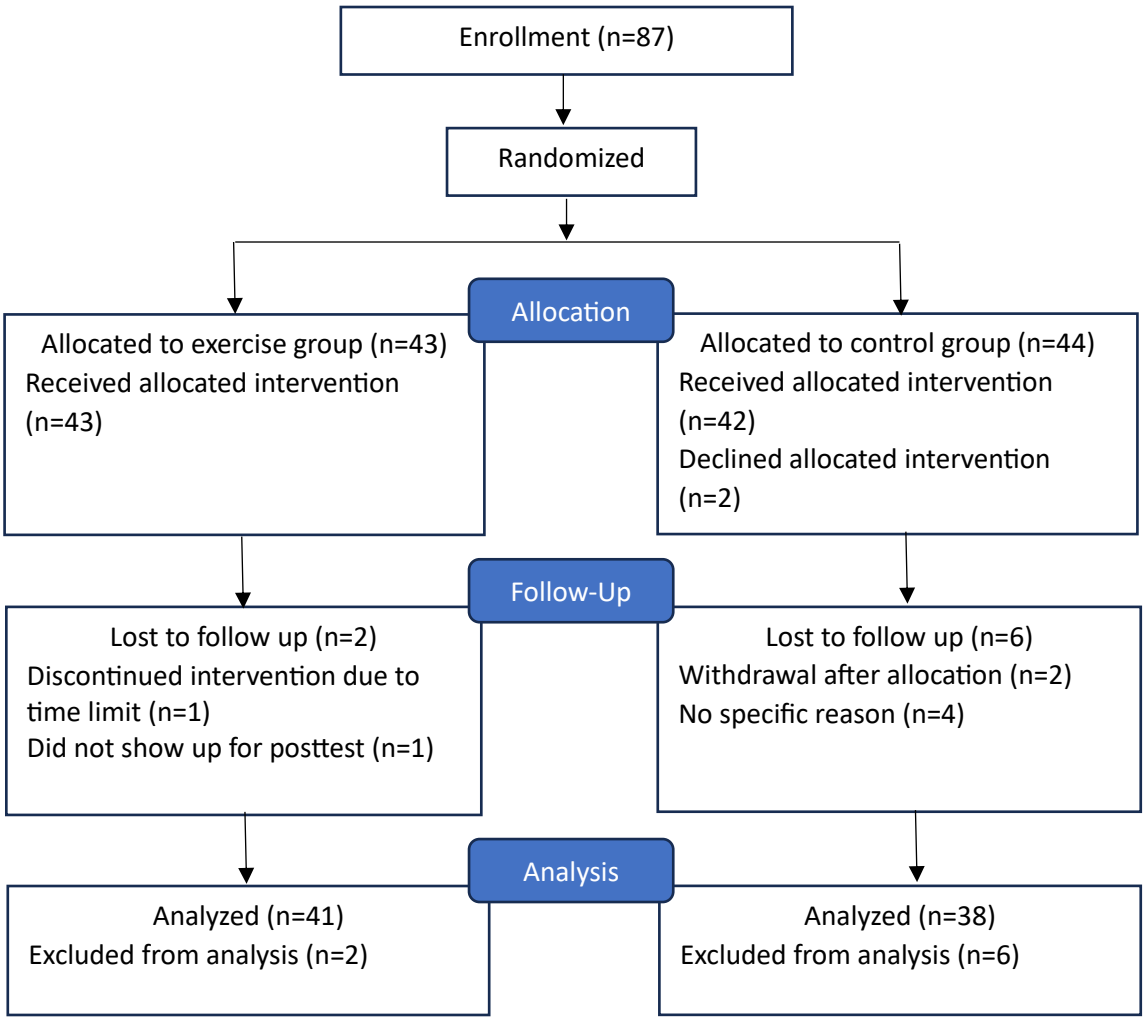


**Figure 1** Consolidated Standards of Reporting Trials (CONSORT) diagram for the two groups in the randomised control trial.

## Adverse effects and safety

An initial prescreening was performed to exclude patients with chronic coronary syndrome and severe comorbidities by following a protocol modified from the European Society of Cardiology's (ESC) guidelines.[25] At the screening visit at the Sahlgrenska University Hospital, the patient's medical health status was assessed, and disease activity was evaluated by a rheumatologist, followed by a cardiopulmonary exercise test (CPET) further screening of contradictions to participate in high-intensity exercise.[25] Adverse effects during exercise were defined as severe symptoms related to the cardiopulmonary system, that is, exercise-induced chest pain, palpitation/arrhythmias, dyspnoea, nausea, dizziness or severe discomfort. Also, increased pain which could be related to exercise or increased disease activity was reported.

## Exercise intervention

The exercise protocol is described in detail in table 1. Patients allocated to the intervention group (IG) participated in 12-week exercise intervention, following the American College of Sports Medicine (ACSM) recommendations for cardiorespiratory and muscle strength exercise.[26] The supervised exercise was conducted in a hospital setting, in groups of eight. Two sessions per week were supervised face-to-face by a physiotherapist, and one aerobic session (70% HRmax) of the patient's own choice per week was non-supervised. The heart rate (% HRmax) during all cardiorespiratory exercises was monitored continuously with an individual heart rate sensor (Polar H10) strapped around the chest and connected to an exercise application (Polar Beat) on the patient's cellphone.

The HIIT sessions on cycle ergometers included high-intensity bouts (90–95% HRmax) alternated with periods on lower intensity (70% HRmax), repeated four times. The intensity of the cardiorespiratory exercise was gradually increased to the pulse target zone over the first 2 weeks, depending on the participant's adaptation to the HIIT protocol.

This was directly followed by strength exercise involving large muscle groups, for 20 min: eight exercises were performed with free weights, weight machines and body weight. The dose was 2–3 sets, 8–10 repetitions, at 70–80% of one repetition maximum (1RM). A progression of the workload was performed following a standardised protocol.

Th exercise was individually tailored based on the patient's physical capacity and physical ability and modified according to present symptoms and health at the time of each session. Rated pain ≤5 on a Visual Analogue Scale (VAS) (0–10) was considered

**Table 2** Baseline demographic and clinical characteristics for the intervention group and the control group with rheumatoid arthritis

| | Intervention group (n=43) | Control group (n=44) | P value |
|---|---|---|---|
| Sex, women/men | 37 (86.0%)/ 6 (14.0%) | 36 (81.8%)/8 (18.2%) | 0.59 |
| Age, years | 48.4 (10.1) | 47.9 (9.3) | 0.83 |
| Disease duration, years | 6.1 (4.58) | 6.9 (5.37) | 0.44 |
| Civil status | | | 0.59 |
| Married, cohabitant | 29 (67.4%) | 32 (72.7%) | |
| Employment status | | | 0.57 |
| Working | 41 (95.3%) | 42 (95.4%) | |
| Studies | 1 (2.2%) | | |
| Education, years | | | 0.94 |
| ≤12 years | 14 (32.6%) | 13 (29.5%) | |
| Postgraduate high school | 4 (9.3%) | 4 (9.1%) | |
| College, University | 25 (58.1%) | 27 (61.4%) | |
| Tobacco | | | 0.64 |
| Current smoker | 6 (14.3%) | 8 (18.6%) | |
| Former smoker | 10 (23.8%) | 7 (16.3%) | |
| MVPA, hours/week | 2.1 (1.58) | 3.1 (2.97) | 0.34 |
| $VO_2$max, mL/kg/min | 26.2 (5.3) | 26.4 (6.5) | 0.87 |
| Grip strength | 214.6 (78.1) | 213.1 (87.4) | 0.92 |
| 1-minute STS | 23.7 (5.5) | 25.0 (6.4) | 0.31 |
| Anthropometry | | | |
| BMI, kg/m$^2$ | 27.1 (5.3) | 27.1 (5.3) | 1.0 |
| Length, cm | 171.5 (7.8) | 169.8 (9.7) | 0.36 |
| Weight, kg | 79.4 (15.2) | 78.5 (19.1) | 0.80 |
| Waist circumference | 89.7 (13.6) | 89.1 (15.2) | 0.83 |
| Disease activity | | | |
| DAS28 | 2.0 (0.90) | 2.0 (1.18) | 0.83 |
| Tender joints | 0.6 (1.91) | 1.0 (4.30) | 0.29 |
| Swollen joints | 0.8 (1.59) | 0.5 (1.00) | 0.29 |
| ESR, mm/hour | 11.0 (11.2) | 11.7 (10.1) | 0.75 |
| CRP, mg/L | 2.2 (3.00) | 2.3 (3.07) | 0.90 |
| VAS-global | 21.1 (18.2) | 18.5 (19.0) | 0.51 |
| VAS-pain | 20.2 (17.6) | 20.1 (20.1) | 0.97 |
| Medication | | | |
| Conventional DMARD | 34 (79.1%) | 32 (72.7%) | 0.49 |
| Biological DMARD | 23 (53.5%) | 21 (47.7%) | 0.59 |
| Targeted synthetic DMARD | 4 (9.3%) | 3 (6.8%) | 0.67 |
| Corticosteroids (oral) | 1 (2.3%) | 2 (4.5%) | 0.57 |
| NSAID | 17 (39.5%) | 18 (40.9%) | 0.90 |
| Anti-hypertensives | 4 (9.3%) | 4 (9.1%) | 0.97 |
| Statins | 1 (2.3%) | 1 (2.3%) | 0.99 |

Values are presented as mean (SD) and number (%).
BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; 1-minute S-T-S, 1-minute sit-to-stand test; MVPA, leisure time physical activity on moderate-to-vigorous intensity; NSAID, non-steroidal anti-inflammatory drug; VAS, Visual Analogue Scale; $VO_2$max, maximal weight corrected oxygen uptake.

acceptable during exercise. Temporary workload modification was made if pain was >5 or persisted for more than 24 hours. In case of a rheumatological 'flare-up' or exacerbation, (eg, joint effusions), the patient was referred to the rheumatology department for consultation.

Adherence to the exercise protocol and the non-supervised sessions, duration and HRmax was recorded in the patient's exercise diary. The details were discussed with the physiotherapist at the following supervised session. Attendance at the supervised sessions was registered by the physiotherapist.

Four physiotherapists with an expertise in rheumatology and trained in cardiopulmonary resuscitation supervised the exercise. Before startup, the physiotherapists attended a 6-hour education session on the exercise intervention, motivational support[27] and self-efficacy approach[28] and were given a treatment manual to follow.

## Control group

Patients allocated to the control group (CG) received individual information of the general health recommendations for physical activity, with encouragement to be physically active on moderate intensity level ≥150 min/week. A home exercise programme was provided, and verbal and written instructions were given (table 1).

All patients received standard outpatient care during the study period at their respective hospitals.

## Outcomes

Outcomes were assessed at baseline and immediately after the intervention at 3 months and included questionnaires addressing demographics, comorbidities, medication use and overall health, along with a medical examination, performance-based tests and blood samples. All assessors including physicians, physiotherapists, nurses and testing personnel for the CPET were blinded to group allocation.

### Primary outcome and end criteria

Changes in cardiorespiratory fitness, $VO_2$max (mL/kg/min), were selected as primary outcome. Cardiorespiratory fitness was assessed with a CPET on a bicycle ergometer, the standard procedure in Sweden. Weight-adjusted $VO_2$max (mL/kg/min) was obtained during progressively increasing workload, during which gas exchange was analysed, following a protocol modified from the American Heart Association (AHA) guidelines.[29] Simultaneously, recording of 12-lead ECG data, heart rate, blood pressure and rating scores of symptoms (BORG CR-10 scale) was assessed. A respiratory exchange ratio ($VCO_2/VO_2$) ≥1.10 in combination with a plateau in $VO_2$ despite increased workload was used as the criterion for reaching $VO_2$max. $VO_2$max was calculated as the mean of the three highest consecutive 10-second measurements. The maximal obtained heart rate during the test was used as a reference during the cardiorespiratory exercises.

### Secondary outcomes

$VO_2$ (mL/min) and ventilatory maximum (VEmax, L/min) were assessed, oxygen pulse ($O_2$-pulse) representing the product of ventricular stroke volume was calculated using the following formula: $VO_2$ mL/min divided by HRmax.[30] Resting blood pressure was recorded with an ambulatory blood pressure monitor with the patient in a seated position, where the lowest value out of two was recorded.

The 1-minute sit-to-stand test was used to assess muscle strength and endurance of the lower extremities.[31] The number of completed rises from a standard chair in 60 s was recorded. Isometric handgrip strength was measured with a digital electronic dynamometer, the Grippit (AB detector, Gothenburg, Sweden), which measures grip strength in newtons (N).[32] The average mean grip strength was used for assessment. Handgrip strength has been found to be associated with shoulder-arm

**Table 3** Changes in primary outcome from baseline (BL) to 3 months (3M) follow-up between the groups for the patients with rheumatoid arthritis

| | Intervention group (n=43) | | Control group (n=44) | | Between group | |
|---|---|---|---|---|---|---|
| | BL Means (SD) | 3M Means (SD) | BL Means (SD) | 3M Means (SD) | LS means difference of change BL to 3M (95% CI) P value | Effect size |
| $VO_2$max, mL/kg/min* | 26.2 (5.30) | 29.2 (6.70) | 26.4 (6.50) | 25.7 (5.90) | 3.71 (2.16 to 5.25) <0.0001 | 1.06 |
| ITT | | | | | | |
| $VO_2$max, mL/kg/min† | | | | | 3.71 (2.16 to 5.25) <0.0001 | |
| Per protocol | | | | | | |
| $VO_2$max, mL/kg/min‡ | 26.8 (5.30) | 30.1 (6.60) | 26.4 (6.50) | 25.7 (5.90) | 4.1 (2.43 to 5.77) <0.0001 | 1.14 |

Values are shown as mean and SD, unless indicated otherwise.
*Primary analysis adjusted for BL age, $VO_2$max and sex.
†Multiple stochastic imputation of 100 dataset adjusted for the minimisation variables.
‡Complementary analysis including patients attending ≥70% of supervised exercise sessions (n=33), adjusted for BL age, $VO_2$max and sex.
$VO_2$max, weight-corrected maximal oxygen uptake.

strength in RA[33]; thus, handgrip strength was used as a surrogate measure to reflect the strength of the upper extremity.

Anthropometry was assessed with waist circumference, body weight and body height. Body mass index (BMI) (kg/m$^2$) was calculated.

Blood samples were drawn after 8 hours of fasting. Lipid status was assessed by serum levels of triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol (TC). Inflammatory markers were assessed by high sensitivity C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Disease activity was estimated with the Disease Activity Score (DAS28), based on clinical assessment of 28 joints (swollen and tender), patient's rating of health (VAS) and ESR.[34] A DAS28 score≥2.6<5.1 indicates low-to-moderate disease activity and <2.6 indicates remission.

Physical activity at baseline was assessed with the Leisure Time Physical Activity Instrument, which assesses the amount of physical activity during the last week.[35]

Pain and overall health related to the rheumatological disease during the past weeks were rated on a VAS (0–100 mm), VAS-pain and VAS-global, where a higher score indicates worse pain or health.

Changes in symptoms were assessed with the Patient Global Impression of Change (PGIC) questionnaires.[36]

## Patient involvement

A patient research partner from the Swedish Rheumatism Association was involved in the study design, the prescreening questionnaire and choice of outcome measures.

## Equity, diversity and inclusion

Our clinical trial includes women and men with RA of different ages and demographics. All eligible patients were considered for participation. More women than men volunteered to participate. While no diversity in study population was planned to balance for gender, ethnicity, socioeconomic level or representation from marginalised groups, the recruitment area encompassed a broad range of socioeconomic groups. We acknowledge that our study excluded patients with such physical disabilities and comorbidities precluding participation in high-intensity exercise. Our research and author team includes both women and men from different professional disciplines and levels.

## Randomisation

Randomisation was performed after screening and enrolment, with optimal allocation (minimisation) using a computerised algorithm in order to balance for sex, age, $VO_2$max (mL/kg/min) and study site. Patients were informed of their group allocation by the physiotherapist supervising the exercise.

## Statistical analyses

Descriptive statistics are presented as mean and standard deviation (SD), frequency and percentages. Comparisons between groups were performed with the Fisher's non-parametric permutation test for continuous variables and Manthel-Haenszel $\chi^2$ test for categorical variables. The main statistical analysis was the analysis of covariance (ANCOVA) of the change for the primary outcome, adjusted for baseline variables for age, $VO_2$max and sex. Primary efficacy analyses were performed on intention-to-treat (ITT) population using multiple imputation for missing values. The effect size was calculated as Cohen's d coefficient. A per protocol analysis on patients in the IG that followed ≥70% of the supervised exercise sessions and the patients in the CG was conducted for primary and secondary outcomes. An exploratory interaction analysis was conducted with the primary effect variable as dependent and the interaction between randomised groups and selected baseline variables. Additionally, an unadjusted analysis was conducted for comparisons between groups based on sex for key outcomes. All tests were two-tailed and conducted at 0.05 significance level. All analyses were performed using SAS V.9.2 (Cary, North Carolina, USA).

## Sample size

To achieve 80% power to detect 10% difference of change in weight-adjusted $VO_2$max with a baseline value of 34.5 mL[37] and estimated SD difference of 5.0, at 5% significance level, a total of 70 patients were needed. To compensate for a dropout rate of 20%, 88 patients were aimed to be recruited.

# RESULTS

In total, 87 patients were included in the study (figure 1), of whom 23% had a low-to-moderate disease activity and 77%

**Table 4** Changes in secondary outcomes from baseline to 3 months follow-up between the groups for the patients with rheumatoid arthritis

| | Intervention group (n=43) | | Control group (n=44) | | Between group | |
|---|---|---|---|---|---|---|
| | BL Means (SD) | 3 months Means (SD) | BL Means (SD) | 3 months Means (SD) | Mean difference of change BL to 3 months (95% CI) P value | Effect size |
| $VO_2$, mL/min | 2047.0 (435.0) | 2282.0 (576.0) | 2013.0 (569.0) | 1988.0 (579.0) | 260.6 (168.5 to 351.5) <0.001 | 1.31 |
| $O_2$-pulse, mL/beat/min | 11.8 (2.5) | 13.3 (3.4) | 11.9 (3.1) | 12.1 (3.4) | 1.38 (0.85 to 1.91) <0.001 | 1.19 |
| VEmax, L/min | 86.1 (18.4) | 91.1 (21.3) | 82.1 (22.2) | 81.2 (24.9) | 6.73 (1.21 to 12.20) 0.016 | 0.57 |
| RER | 1.2 (0.09) | 1.17 (0.09) | 1.2 (0.09) | 1.2 (0.10) | −0.01 (−0.04 to 0.02) 0.45 | 0.17 |
| HRmax, beats/min | 173.4 (11.5) | 172.1 (11.8) | 169.4 (16.5) | 164.8 (16.3) | 1.56 (−1.79 to 4.84) 0.37 | 0.57 |
| Systolic BP | 123.0 (17.8) | 120.7 (16.6) | 123.9 (15.9) | 124.4 (17.7) | −1.98 (−7.74 to 3.79) 0.49 | 0.16 |
| Diastolic BP | 74.8 (12.1) | 73.3 (10.2) | 74.5 (10.5) | 75.4 (11.3) | −1.72 (−5.00 to 1.56) 0.31 | 0.23 |
| Grip strength, N | 214.6 (78.1) | 249.8 (89.6) | 213.1 (87.4) | 216.8 (93.0) | 28.5 (3.80 to 52.80) 0.021 | 0.52 |
| 1-minute STS, no | 23.7 (5.5) | 30.4 (5.3) | 25.0 (6.4) | 25.9 (6.7) | 5.0 (3.35 to 6.72) <0.001 | 1.33 |
| Anthropometry measure | | | | | | |
| Weight, kg | 79.4 (15.2) | 78.9 (14.6) | 78.5 (19.1) | 78.2 (19.2) | −0.44 (−1.32 to 0.44) 0.33 | 0.23 |
| BMI, $kg/m^2$ | 27.1 (5.3) | 27.0 (5.1) | 27.1 (5.3) | 26.9 (5.1) | −0.13 (−0.43 to 0.17) 0.39 | 0.20 |
| Waist circumference, cm | 89.7 (13.6) | 86.8 (11.6) | 89.1 (15.2) | 88.7 (14.4) | −2.60 (−5.09 to −0.18) 0.035 | 0.47 |
| Serum lipids | | | | | | |
| S-TC, mm/L | 5.30 (1.32) | 5.20 (1.31) | 5.16 (1.00) | 5.22 (0.95) | −0.14 (−0.35 to 0.08) 0.21 | 0.29 |
| S-HDL, mm/L | 1.61 (0.40) | 1.61 (0.37) | 1.58 (0.39) | 1.59 (0.39) | −0.02 (−0.10 to 0.07) 0.72 | 0.08 |
| S-LDL, mm/L | 3.58 (1.19) | 3.45 (1.20) | 3.45 (0.89) | 3.47 (0.78) | −0.08 (−0.27 to 0.10) 0.39 | 0.20 |
| S-TG, mm/L | 0.92 (0.42) | 0.95 (0.42) | 0.99 (0.42) | 0.95 (0.38) | 0.01 (−0.11 to 0.13) 0.88 | 0.04 |
| Disease activity | | | | | | |
| DAS28-ESR | 2.0 (0.90) | 2.0 (0.82) | 2.0 (1.18) | 2.3 (1.33) | −0.25 (−0.60 to 0.10) 0.16 | 0.32 |
| ESR | 11.0 (11.2) | 12.2 (10.4) | 11.7 (10.1) | 13.5 (11.4) | −0.64 (−3.23 to 1.90) 0.64 | 0.11 |
| CRP | 2.2 (3.00) | 2.4 (3.49) | 2.3 (3.07) | 2.82 (3.33) | −0.21 (−1.56 to 1.16) 0.77 | 0.07 |
| VAS-global, 0–100 | 21.1 (18.2) | 18.3 (16.8) | 18.5 (19.0) | 29.5 (26.9) | −14.7 (−23.8 to −5.5) 0.001 | 0.72 |
| VAS-pain, 0–100 | 20.2 (17.6) | 19.5 (17.1) | 20.1 (20.1) | 21.6 (22.4) | −4.0 (−13.07 to 5.06) 0.38 | 0.20 |

Values are shown as mean and SD, unless indicated otherwise.
Missing values at month 3 in total for the IG (n=2); missing values at month 3 in the CG; CRF (n=8), BP (n=6), grip strength (n=6), STS (n=6), serum lipids (n=6), body measures (n=6), DAS28 (n=7), ESR and CRP (n=6), VAS-global and VAS-pain (n=7).
BMI, body mass index; BP, blood pressure at rest; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; HRmax, maximal heart rate; 1-minute STS, 1-minute sit-to-stand test; $O_2$-pulse, oxygen pulse; RER, respiratory exchange ratio; Serum levels of S-TG, triglycerides; S-HDL, high-density lipoprotein; S-LDL, low-density lipoprotein; S-TC, total cholesterol; VEmax, ventilatory maximal; $VO_2$, mL/min, maximal oxygen uptake.

were in remission, at baseline. The disease activity did not change during the study. The groups were considered similar in demographic and clinical characteristics at baseline (table 2).

## Adherence

The patients in the IG attended an average of 19 (SD 6.0) supervised sessions and performed an average of 12 (SD 3.6) self-administered sessions. A total of 33 patients in the IG followed ≥70% of the supervised exercise sessions. The dropout rate during the intervention period was eight in total, seven women and one man, all significantly younger than the rest of the study population. In the IG, one patient discontinued the study after attending the first supervised session and one patient did not show up for post-test at month 3. In the CG, two withdrew

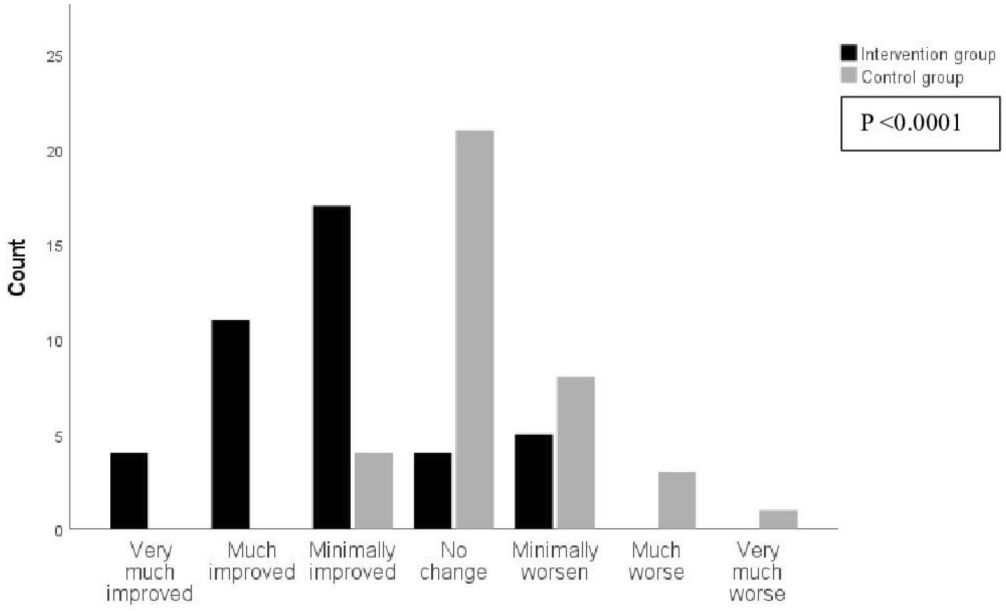


**Figure 2** Rating of Patient's Global Impression of Change after 12 weeks for the intervention group and the control group.

when receiving group allocation and four did not show up for post-test (figure 1).

### Adverse effect and safety

In the IG, one patient experienced irregular heart rate during a supervised HIIT session. After consultation with the cardiologist and referral to UCG for evaluation of arrythmia, the patient could complete the intervention at moderately intensive level. Four patients encountered temporarily increased musculoskeletal pain during the strength exercise, which was managed with temporary exercise modification. One patient experienced persistent musculoskeletal pain after half of the intervention period and completed the intervention without the strength exercise. Two patients received a corticosteroid injection each, one in the ankle and one in the wrist, followed by temporary exercise modification.

### Primary outcome

A significant mean group difference of change was found for $VO_2$max (3.71 mL/kg/min, 95% CI 2.16 to 5.25, p<0.0001) where the IG showed significant improvements compared with the CG, adjusted for sex, age and baseline $VO_2$max. The sensitivity analysis on the ITT population revealed an equal mean difference of change for $VO_2$max between the groups (table 3).

### Secondary outcomes

A significant mean group difference of change was found for $VO_2$ mL/min and $O_2$-pulse (p<0.0001) in favour of the IG (table 4). A significant mean group difference of change was also found for handgrip strength (p=0.021) and leg muscle strength (p<0.001) where the IG had a better muscle function compared with the controls. In addition, a significant mean group difference of change was found for waist circumference (p=0.035) and overall health (p=0.001) in favour of the IG (table 4). The PGIC rating was significantly different (p<0.0001) between the groups at month 3, with very much to minimally improved symptoms among 78% in the IG and 11% in the CG (figure 2).

The exploratory interaction analysis is presented in online supplemental table 4.

### Per protocol analysis

The per protocol analysis for the primary outcome variable adjusted for sex, age and baseline $VO_2$max revealed a significant mean group difference of change for $VO_2$max (4.1 mL/kg/min; 95% CI 2.43 to 5.77), p<0.0001 in favour of the patients that followed ≥70% of the supervised sessions (table 3). For the per protocol analyses of the secondary outcomes, see online supplemental table 5. The subgroup analysis of key outcome variables based on sex is presented in online supplemental table 6.

## DISCUSSION

The 12-week intervention of HIIT and strength exercise showed beneficial treatment effects on patients' cardiovascular health in terms of significant improvements in $VO_2$max, $O_2$-pulse and reduction in abdominal fat. Moreover, significant treatment effects were also found on muscle strength and overall health, showing additional beneficial health effects for the patients in the IG. Importantly, the disease activity and pain did not deteriorate, implying a tolerance to the exercise protocol.

The mean treatment effect of 3.71 mL in $VO_2$max indicates substantial health-related gains for the patients in the IG since the risk of all-cause mortality and CVD mortality has been found to be decreased by 12–13%[38 39] and 13%, respectively,[38] per increase in 3.5 mL/kg/min of $VO_2$max. The treatment effect in $VO_2$max is comparable with the findings from two previous studies of axial spondyloarthritis[40] and psoriatic arthritis[41] (2.7–3.7 mL/kg/min), with similar cardiorespiratory exercise intensity and volume. Compared with our findings, a study conducted in patients with RA reported a smaller treatment effect on $VO_2$max after 20 weeks of cardiorespiratory and strength exercise, three times per week.[42] The differences could partly be attributed to the intensity of the cardiorespiratory exercise since this was lower compared with the one in our study. In the present study, the observed increase in $VO_2$max average in the IG correspond to a 11% improvement (12.6% difference in change between the groups), implying a clinically relevant effect. Additionally, the improvement in $VO_2$max was accompanied by increase in $O_2$-pulse which has been found

to reflect increased left ventricular stroke volume,[43] a key factor when $VO_2$max is improved from cardiorespiratory exercise on a high intensity.[44]

The mean treatment effect on waist circumference indicates a reduction of abdominal fat, thereby loss of visceral fat mass in the IG. Although an indirect measure, a reduction of >2 cm in waist circumference is found to improve metabolic health profile even in the absence of weight loss.[45] Exercise has the potential to reduce visceral adiposity in a dose-dependent manner, and both cardiorespiratory and strength exercise have shown to reduce body fat mass.[46 47] The improvement by 16% in upper body strength and 30% in lower body strength in the IG point to a reduction in body fat mass and gain in muscle mass, align with the findings of a study with progressive strength exercise in RA.[48]

No major effects were found in serum lipids after 3 months. One explanation could be that the lipids were already within recommended levels at baseline and therefore the potential for improvement in these measures was limited. Our findings are in agreement with a recently published study of HIIT with well-controlled patients with inflammatory joint diseases.[49] Still, HIIT has been found to improve the lipid profile in other non-rheumatic populations.[50 51] Moreover, a non-randomised study of patients with RA reported improvement in blood lipids after 6 months with cardiorespiratory and resistance exercise, indicating that the duration of the intervention is also critical for possible changes in lipids.[52] Thus, the potential effects of HIIT on lipid status in rheumatic diseases warrant more research with interventions of longer duration.

Overall health remained stable in the IG while it decreased in the CG. These findings together with a significant improvement in patients' impression of change for the IG support the positive findings of the exercise intervention on the patients' overall well-being and health.

No adverse effects were reported except a temporary increase in musculoskeletal pain for a few patients in the IG. Moreover, the adherence to the protocol must be considered as satisfactory where almost 80% of the patients followed ≥70% of the supervised sessions. Importantly, the treatment effect on $VO_2$max (4.1 mL/kg/min) was even larger for the patients that followed the protocol. Our results support the evidence of HIIT as a superior method to maximise $VO_2$max[18] and add to the evidence for structured exercise on CVD managements in RA.[8]

### Strength and limitations

A major strength of this study is the randomised controlled design, blinding of all assessors for group allocation, objective measure of cardiorespiratory fitness and the exercise protocol, individually tailored based on the patient's physical capacity and ability. Also, a strength is that the IG was compared with an active CG who received counselling on the general recommendations for physical activity regarding moderate intensity, a level recommended as the minimum to obtain health benefits. However, self-administered physical activity was not reported in the CG which is a limitation. The 1-minute sit-to-stand test does not predominantly assess muscle strength which could be considered a limitation. However, the test was chosen as it is easily applicable in a clinical setting with no requirement of advanced laboratory equipment. The majority of the study patients were in remission or had a low disease activity which is consistent with modern pharmacological treatment in RA, indicating a representative study sample.[53] Due to few included men in the study, the results should be interpreted with some caution with regard to men. Nevertheless, the exploratory interaction analysis revealed that men had the highest potential to improve $VO_2$max in the study.

## CONCLUSIONS

The supervised exercise intervention for 12 weeks displayed a number of beneficial and clinically significant effects on patients' cardiovascular health, physical fitness and overall health without deterioration in disease activity and pain. HIIT and strength exercise in combination appear to be feasible and well tolerated and could be recommended as a treatment option to improve cardiovascular and physical health in patients with well-controlled RA.

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**Acknowledgements** We wish to thank all patients who participated in the study and the patient research partner for the contribution to the study. We also thank the personnel at the Clinical Rheumatology Research Center at Sahlgrenska University Hospital and the physiotherapists at Sahlgrenska University Hospital and Uddevalla Hospital for their help with exercise supervision. A special thanks to Nils-Gunnar Persson for expert consultation of statistical analyses and Fredrik Edin, Department of Food and Nutrition, and Sport Science, Center for Health and Performance, University of Gothenburg.

**Contributors** AB designed the trial, recruited participants, collected data, analysed and interpreted data, and wrote the manuscript. KM designed the trial, interpreted data and reviewed the manuscript. SS designed the trial, collected data, interpreted data and reviewed the manuscript. JS recruited participants, supervised the exercise group and reviewed the manuscript. EK collected data, interpreted data and reviewed the manuscript. MB designed the trial, interpreted data and reviewed the manuscript. JB designed the trial, recruited participants, collected data, interpreted data and reviewed the manuscript. All authors have approved the final draft to be published. AB is the guarantor of the paper.

**Funding** This work was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (grant numbers ALFGBG-992712, ALGGBG-985902), the Healthcare Board, Region Västra Götaland (grant numbers FOUREG938803, FOUREG967218, FOUREG980124), the Norrbacka Eugenia foundation and the Swedish Rheumatology Association research grant (grant numbers R-931095, R-967316, R-968978, R-980980, R-992689).

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained directly from patient(s).

**Ethics approval** The study protocol and consent documents were approved by the National Ethics Committee in Sweden (Dr nr. 2019-05255). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. The dataset analysed in the present study are available from the corresponding author on reasonable request.

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# Expected benefit of high-intensity interval aerobic exercise program of 3 months for patients with RA: Improve cardiopulmonary function and health. Prevent deterioration in cardiovascular health and quality of life.

**Rheumatoid arthritis** (RA) is a chronic inflammatory disease with 0.7% prevalence rate in Sweden. RA is characterized by symmetrical inflammation of peripheral joints, although larger joints can also be affected. Clinical symptoms of RA are pain, stiffness, fatigue, limited range of motion in joints, and reduced muscle strength. Patients with RA have increased prevalence rates of comorbidities, mainly cardiovascular diseases and atherosclerosis. Despite more effective control of inflammation by improved pharmacological therapies, reduced physical function, cardiovascular disease and increased arterial stiffness remain major problems in RA.

**Cardiovascular disease.** Patients with RA have markedly increased risk for cardiovascular disease, leading to increased mortality[1]. Increased mortality in RA has partially been attributed to cardiac insufficiency and myocardial infarction[1, 2]. Cardiopulmonary and respiratory functions are assessed by means of cardiopulmonary exercise test (CPET). A low maximum oxygen uptake (VO2max) has been suggested a stronger risk factor for cardiovascular disease and mortality than high blood pressure, overweight, smoking, and hyperlipidemia[3].

Patients with RA have lower cardiopulmonary fitness, with a reduction of 20% in VO2max compared to age-matched healthy controls[4]. There can be several reasons for the low VO2max in patients with RA, for example, cardiovascular effects of the inflammatory process. However, a probable reason is low physical activity level of patients with RA. The general recommendation for health-enhancing physical activity is: activity/exercise corresponding to a moderate intensity for ≥150 minutes/week or activity/exercise at vigorous intensity for ≥75 minutes/week[5]. Only 36% of RA patients report physical activity at these levels[6]. Indeed, regular physical activity is a common problem, as only a minority of the Swedish population successfully follow recommendations, when objectively assessed using an accelerometer[7].

**Atherosclerosis** and arterial stiffness are commonly observed in RA [8] and are associated with increased risk of cardiovascular disease. Atherosclerosis in RA is linked to the inflammation driving the rheumatoid disease along with general risk factors, such as low physical activity level, high body mass index (BMI), hypertension and smoking. The gold standard measurement of stiffness in larger arteries is the aortic pulse wave velocity (PWV). Pulse wave velocity increases with age, even in the absence of clinical disease. Studies indicate that aerobic exercise diminishes arterial stiffness[9].

**Metabolic and inflammation profiles.** RA is characterized by chronic inflammation, with increased production of pro-inflammatory cytokines. Adipokines are metabolic and inflammatory factors that are released in adipose tissue. A well-characterized adipokine is leptin, which is associated with disease activity in RA. Reduction of risk in cardiovascular disease through physical activity has been associated with improved inflammatory and lipid profiles and improved insulin resistance. Changes in these metabolic and inflammatory factors will be examined.

**Cardiorespiratory exercise.** Regular physical activity and exercise have been shown to confer multiple health effects and to decrease mortality from cardiovascular diseases, stroke, cancer and diabetes. Therefore, the general guidelines related to physical activity for healthy people are currently also recommended for patients with rheumatic diseases [10] and physically active people with risk of clinical coronary artery disease[11].

**High-intensity interval aerobic exercise.** Physical activity is any bodily movement that increases energy expenditure, while exercise is structured and planned physical activity.

Moderate-intensity aerobic exercise is defined as achieving 60%–74% of the maximum heart rate, while high-intensity level is 75%–94% of the maximum heart rate. High-intensity interval exercise is a relatively new mode of exercise, with alternating short intervals of high and low intensity exercise. The target heart rate during the high-intensity bouts is 90%–95% of the maximum heart rate[12]. This exercise mode has attracted intense interest from the healthy population and among patients with different diseases. One reason for this is that high-intensity exercise is time-efficient and results in a greater improvement in VO2max than moderate continuous exercise[13]. This is important when aiming to prevent cardiovascular disease, since the risks for cardiovascular morbidity and mortality decrease for every increment in 1 ml of VO2max[14].

Exercise interventions for patients with RA are commonly conducted at low or moderate intensities[10], while studies of high-intensity aerobic exercise in RA are scarce. However, a small sample (N=12) with younger (mean age, 33 years) patients with either juvenile RA or RA showed tolerance to high-intensity exercise[15], although no firm conclusions could be drawn.

**Our previous studies** Our long-term goal is to improve cardiopulmonary function and health for patients with rheumatic disease. The proposed project is based on our previous research on physical activity/ exercise in general [7, 11, 14, 16] and in patients with rheumatic diseases in particular[17-19]. We showed that patients with axial spondyloarthritis (axSpA) can manage aerobic exercise at high intensity[18]. VO2max and disease activity scores [18] as well as fatigue, sleep and mood were improved in the patients with axSpA as a result of the high-intensity exercise[20]. All of these benefits are of major importance to cope with rheumatic disease in daily living. The patients reported increased physical activity at a moderate-to-high intensity level at the 1-year follow-up[19], showing that they motivated for long-term exercise, which is an important outcome. Therefore, we deem it important to study the effects and feasibility of high-intensity interval exercise also for patients with RA.

A pilot study (n=4) was conducted, and it showed positive response of patients with RA engaged in in HIIT program. All patients managed the high intensity exercise level. As patients with RA have an increased risk of cardiovascular disease, and exercise at a high intensity can involve greater risks[11, 16], their risk profile will be taken to account. We will examine the patients using the European Sport Cardiology algorithm, designed for risk evaluation of patients with risk of cardiovascular disease[11]. Pedagogic modes, such as person-centered guidance [17] and motivational support[18, 19], which have previously been shown to contribute to successful outcomes, will be applied in the planned study.

**The overarching objective of this study** is to evaluate the effects of high-intensity interval aerobic training (HIIT) and strength exercise on cardiovascular health, physical fitness and general health for patients with RA who are receiving the standard of care.

**We hypothesize** that a 12-week high-intensity interval exercise program will provide substantial improvements in the cardiovascular health, physical fitness and general health of patients with rheumatoid arthritis (RA).

**Study design.** A randomized controlled intervention trial (0–12 weeks).

**Patients**

**Criteria for inclusion.** Patients with established RA diagnosed according to ACR/EULAR 1987/2010 criteria, which comprise clinical examinations of joints, radiological and laboratory measurements. Disease duration >1 year, age range 20–60 years, stable medication on anti-rheumatic drugs for >3 months, and low-to-moderate disease activity (<5.1) according to the Disease activity score 28 (DAS28).

**Criteria for exclusion.** To cater for the safety of patients participating in this study, it is necessary to exclude patients with other severe diseases that may be associated with adverse events or restrict participation in high-intensity exercise, such as cerebrovascular diseases,

diabetes, severe hypertension, chronic obstructive pulmonary disease, and other severe pulmonary diseases[11, 16]. Screening for exclusion criteria is conducted in several phases of the examination, and include electrocardiogram, CPET, and pulse wave velocity test. Other exclusion criteria are arthroplasty of large joints, inability to manage exercise test (CPET), pregnancy, already participating in regular aerobic or strength exercise at high intensity for >1 hour/ week during the last 6 months, inability to speak or read Swedish.

**Procedure**

**Recruitment**. In total, 88 patients (see power calculation) with established RA will be recruited from the rheumatology units at Sahlgrenska University Hospital in Gothenburg and Mölndal, Uddevalla Hospital through the Swedish Rheumatology Quality Register (SRQ).

Oral (by telephone) and written information about the study will be presented to potential participants. Screening will involve assessment of inclusion and exclusion criteria for each subject, according to previously established screening protocol for risk factors of cardiovascular diseases before participation in sports or intense exercise[11, 16]. Those fulfilling criteria will be invited to Clinical Rheumatology Research unit at Sahlgrenska University Hospital. Information about age, gender, disease duration, and pharmacologic treatments will be gathered through structured interviews, medical records and SRQ.

Clinical examinations by a rheumatologist will comprise the general health status and evaluations of rheumatoid disease and comorbidities. Blood samples will be taken, and an electrocardiogram (ECG) will be conducted. A physical assessment with submaximal bicycle test and muscle function will be conducted to determine if the patient can manage the maximal CPET. Patients will be asked to fill in a battery of questionnaires. Thereafter, patients will be referred for the CPET of VO2max and the PWV test for screening for risk of adverse events.

**Statistics.** To achieve 80% power to detect 10% difference in change between the groups in VO2max, a total of 77 participants needs to be recruited. The calculation of baseline (34 ml/min and SD of difference: 5.0) is based on a previous study (Bilberg, Rheumatol 2005). A total of 88 patients will be recruited to compensate for 20% dropouts. Within- and between-group differences will be analyzed by parametric statistics. If major deviations within the normal range are detected, we will consider data transformation or non-parametric statistics. A statistical advisor will be consulted for all the analyses.

**Randomization** will be conducted in blocks of four subjects by a computer-generated sequence prepared by a statistician. Concealed, sequentially numbered, sealed, opaque envelopes will be opened by a person not involved in the examinations or treatments, who will also inform regarding the group to which the participant is allocated.

**Control group** (0-12 weeks)

Participants in the control group meet a physiotherapist for one session to introduce the general health recommendations for physical activity [5] and encourage physical activity on moderate intensive level ≥150 minutes/week. Participants are introduced to a home exercise program for improvement of muscle function and balance during the intervention period [5, 17]. Verbal and written instructions are given, according to previous used model[17].

**Intervention** (0-12 weeks)

The program includes 12 weeks of aerobic and resistance exercises. Two sessions/week are supervised by an experienced physiotherapist, while a third additional session is non-supervised session of the patient´s own choice. The target of the HIIT intervals is 90%–95% of maximum heart rate (13), based on measured maximum heart rate obtained during CPET at baseline. The high-intensity intervals are alternated with recovery phases at 70% of max heart rate. The exercise protocol comprises 10 minutes of warm-up, followed by 25 minutes of exercise, comprising 4 intervals of 4-minute bouts of high-intensity exercise and 3 intervals of 3-minute bouts of active recovery. The session ends with cooling down for 3–5 minutes.

The exercise is initiated with an individual session, at moderate exercise intensity, progressing to high intensity according to individual capacity. Exercise sessions are modified according to present health at the time of the session (actual symptoms, lack of energy, stress, etc.). Exercise guidance follows principles of self-efficacy and person-centeredness, applying supervision, identification of possible limitations and barriers, exercise diary, a portable heart rate monitor, and continuous dialogue with individual feed-back by a physiotherapist.

Thus, the exercise program is continuously monitored, adapted to each participant and conducted with rigorous guidance, whereby a physiotherapist follows each patient´s heart rate, symptoms, and perceptions. An individual heart rate sensor (Polar H10) connected to a training application loaded in the patient´s cellphone (Polar Beat) and used at each exercise session for monitoring heart rate. Two physiotherapists trained in cardiopulmonary resuscitation (CPR) are present at each session for safety reasons. A mobile intensive care group from the intensive care unit is available less than 5 minutes away from the exercise facilities at the hospitals. Resistance exercise sessions of 20 minutes each include large muscle groups in lower and upper extremities and trunk: 8–10 repetitions with 2–3 sets, with or without equipment.

**Primary outcome**

*Cardiopulmonary function* (0 -12 weeks) is assessed by weight adjusted VO2max (ml/kg/min), obtained during progressively increasing work on a bicycle, during which gas exchange will be analyzed, called the cardiopulmonary exercise test (CPET)**.** Registration of ECG data, heart rate and blood pressure will be conducted. A well-established clinical protocol will be applied, and this test is the gold standard when measuring improvement in physical capacity and is directly related to cardiovascular function. The test will be performed in the SU/Clinical Physiology laboratory, as a previous exercise study, for safety reasons and as an outcome measure [17].

**Secondary outcomes**

*Metabolic factors* (0-12 week). Lipid status is assessed by changes in blood levels of triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol. Blood samples are drawn after eight hours of fasting.
*Physical function* (0-12 week). Muscle function will be assessed using the 1-minute Sit-to-Stand test and using a dynamometer to measure the grip strength of the hand. Both tests are reliable and have been validated for patients with RA.
*Anthropometry measurements* (0-12 weeks) will be assessed with body weight and body height, BMI-score (kg/m2) and waist circumference.
*Resting blood pressure* is recorded with an ambulatory blood pressure monitor with the patient in a seated position, where the lowest value out of two was recorded.
*Disease activity* (0-12 week) measured using DAS28, a gold standard in rheumatology, based on clinical assessment of 28 joints (swollen, tender), patients´ rating of health (VAS), and sedimentation rate (ESR). A score <5.1 indicates low-to-moderate disease activity and <2.6 indicate remission.
Patient-administered questionnaires on health, symptoms and physical activity are well-established, reliable and valid instruments for patients with RA, and they have been applied in our previous studies.
*Pain and global health* (0-12 week) are rated on a Visual Analogue Scale (VAS).
*Physical activity* (0-12 week) is reported on a standardized questionnaire, called the Leisure Time Physical Activity instrument (LTPAI).
*Changes in symptoms* (12-week) is assessed with the patient global impression of change (PGIC) questionnaires.
*Feasibility* has previously been evaluated as adherence to the exercise protocol [10]. In this study, will document: all the reasons for declining to participate and for exclusions during the screening process, attendance at exercise sessions; adherence to the study protocol (maximum heart rate, average heart rate); and possible adverse effects.

**Ethics**

Rigorous control of safety is applied during the screening process as well as when planning and

leading the exercise. Integrity of patients is protected by coding and anonymizing the data. An application to the National Ethics Committee in Sweden will be submitted for approval of the study plan. Data Protection Office at SU will be contacted for GDPR. Incidental findings with regard to cardiovascular health will be remitted to the Cardiology clinic by JB. Other unexpected findings related to the subjects´ health will be addressed by JB who will contact the relevant specialist clinic or general practitioner. JB will contact the Rheumatology clinic of the patient regarding unexpected findings relating to the patient's rheumatic disease.

**Research environment and Research facilities relevant to the project**
The research team combines three units at the University of Gothenburg (GU), The Sahlgrenska Academy: 1) Institute of Neuroscience and Physiology, Section of Health and Rehabilitation (KM, AB); 2) Institute of Medicine, Department of Molecular and Clinical Medicine (SS, MB); and 3) Institute of Medicine, Department of Rheumatology and Inflammation Research (JB). The clinical units are Rheumatology/SU, Physiotherapy/SU and Rheumatology/Uddevalla.

*Coordination.* The recruitment will be conducted by Annelie Bilberg and Jan Bjersing together, with tight weekly cooperation. AB will coordinate the examinations and the treatments both for the intervention- and control group. Site visits will be conducted, and telephone meetings will be held each or each other week.

*Clinical environment.* Patients will be recruited from rheumatology units at Sahlgrenska University Hospital (SU), and from Uddevalla hospitals. Clinical examinations are conducted at the Clinical Research Facility (CRF) in SU/Rheumatology (JB, AB), and at SU/ Clinical physiology laboratory (SS). Exercise interventions are to be conducted at physiotherapy units at SU and Uddevalla hospitals, by using exercise equipment required at these facilities All the physiotherapists will receive appropriate training and education before the start of the project by the project leader (AB).

**Personal resources, competence and role in the project**
**Annelie Bilberg (AB),** Senior Physiotherapist, PhD. Working clinically as a physiotherapist at the rheumatology unit, Sahlgrenska University Hospital, Gothenburg and affiliated to Institute of Neuroscience and Physiology/ Physiotherapy. Coordinator for physiotherapists within rheumatology in the Western region of Sweden, which will facilitate coordination of this study, and long-term implementation of the exercise program in clinic. Clinical expert in exercise and rheumatic disease. Project leader and coordinator of the present study, with responsibility for recruiting the patients, as well as the clinical examinations and coordination of all the examinations and treatments for the participants in the study. She will educate and support the physiotherapists acting as leaders at the three study sites in the Western region of Sweden.
**Jan Bjersing (JB)**, MD PhD, Associate Professor and specialist in rheumatology. JB is employed at SU/Rheumatology, including a 20% adjunct lectureship at GU, The Sahlgrenska Academy. Will be responsible for the recruitment and screening of patients. He has experience from several clinical studies involving studies of biomarkers during exercise.
**Kaisa Mannerkorpi (KM)**, PhD and Professor in physiotherapy at the Institute of Neuroscience and Physiology, Section of Health and Rehabilitation, Unit of Physiotherapy. She has supervised seven previous exercise studies. Expert in personal centered health. She is responsible for the personal centered support for long-term exercise after end of the supervised HIIT in the intervention group.
**Sara Svedlund (SS)**, Care unit Chief Physician, MD, PhD, Associate Professor at the Department of Clinical Physiology/SU, and Institute of Medicine, Department of Molecular and Clinical Medicine. Responsible for the execution, interpretation and analysis of the CPET and PWV data in this study. Runs an academic core laboratory that uses different modalities for cardiovascular characterization.
**Mats Börjesson (MB),** Professor of Sports Physiology and MD, Specialist in Cardiology and Internal medicine. Special research interest in health benefits and potential risks of physical activity and sports (Sports Cardiology). Head of Center for Health and Performance Laboratory at University of Gothenburg, Sweden. He is responsible for the research design

from a cardiological perspective including safety aspects and participates in the analysis of the data.

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Table 4. Exploratory interaction analysis on $VO_2$max for the total study population (N=87) and baseline variables

| | Interaction *p*-value | Mean diff of change (95%CI) | *p*-value |
|---|---|---|---|
| Age | 0.3948 | | |
| Gender | 0.0005 | | |
| Female | | 2.36 (1.13; 3.59) | 0.0003 |
| Male | | 9.67 (4.25; 15.09) | 0.0003 |
| Weight, kg | 0.048 | | |
| ≤70 | | 2.72 (0.82; 4.63) | 0.0069 |
| >70 | | 4.35 (1.91; 6.80) | 0.0008 |
| Length, cm | 0.0002 | | |
| ≤170 | | 1.72 (-0.01; 3.45) | 0.0510 |
| >170 | | 5.74 (3.44; 8.04) | <.0001 |

Interaction analyses between the total study population and baseline variables regarding primary efficacy variable as dependent

Table 5. The per procol analyses for the changes in secondary outcomes from baseline to 3 months follow-up between the groups

| | Intervention group (n=33) | | Control group (n=44) | | Between group | |
|---|---|---|---|---|---|---|
| | BL<br>Means (SD) | 3 Month<br>Means (SD) | BL<br>Means (SD) | 3 Month<br>Means (SD) | Mean diff of change BL to 3M<br>(95% CI)<br>*p*-value | Effect size |
| VO2 mL/min | 2108 (450.0) | 2378 (581.0) | 2013 (569.0) | 1988 (579.0) | 292.1 (195.6; 389.9)<br><0.0001 | 1.45 |
| O2-pulse mL/beat/min | 12.2 (2.6) | 13.9 (3.5) | 11.9 (3.1) | 12.1 (3.4) | 1.61 (1.05; 2.17)<br><0.0001 | 1.39 |
| VEmax L/min | 87.6 (19.3) | 93.5 (22.3) | 82.1 (22.2) | 81.2 (24.9) | 7.21 (1.2; 13.21)<br>0.016 | 0.57 |
| RER | 1.18 (0.08) | 1.15 (0.09) | 1.20 (0.09) | 1.20 (0.10) | -0.016 (-0.04; 0.01)<br>0.018 | 0.59 |
| HRmax, beats/min | 173.9 (11.1) | 171.9 (11.9) | 169.4 (16.5) | 164.8 (16.3) | 0.87 (-2.82; 4.45)<br>0.65 | 0.12 |
| Systolic BP | 124.0 (17.6) | 121.2 (16.4) | 123.9 (15.9) | 124.4 (17.7) | -2.39 (-8.23; 3.47)<br>0.43 | 0.19 |
| Diastolic BP | 74.9 (11.6) | 73.5 (10.3) | 74.5 (10.5) | 75.4 (11.3) | -1.72 (-5.03; 1.58)<br>0.31 | 0.25 |
| Grip strength, N | 228.2 (79.4) | 262.4 (90.7) | 213.1 (87.4) | 216.8 (93.0) | 32.2 (5.2; 58.9)<br>0.02 | 0.56 |
| One-minute STS, no | 25.0 (5.4) | 30.7 (5.1) | 25.0 (6.4) | 25.9 (6.7) | 4.28 (2.60; 5.94)<br><0.0001 | 1.20 |
| Anthropometry | | | | | | |
| Weight, kg | 80.0 (16.5) | 79.5 (15.5) | 78.5 (19.1) | 78.2 (19.2) | -0.55 (-1.47; 0.39)<br>0.24 | 0.28 |
| BMI, kg/m2 | 27.2 (5.8) | 27.0 (5.5) | 27.1 (5.3) | 26.9 (5.1) | -0.17 (-0.48; 0.15)<br>0.29 | 0.26 |
| Waist circumference, cm | 90.9 (14.7) | 87.1 (12.2) | 89.1 (15.2) | 88.7 (14.4) | -3.56 (-6.16; -0.94)<br>0.0098 | 0.64 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Serum lipids | | | | | | |
| S-TC | 5.34 (1.43) | 5.19 (1.41) | 5.16 (1.00) | 5.22 (0.95) | -0.15 (-0.39; 0.08) 0.2 | 0.31 |
| S-HDL | 1.62 (0.41) | 1.61 (0.36) | 1.58 (0.39) | 1.59 (0.39) | -0.02 (-0.11; 0.08) 0.71 | 0.09 |
| S-LDLmm/L | 3.64 (1.26) | 3.45 (1.26) | 3.45 (0.89) | 3.47 (0.78) | -0.11 (-0.31; 0.1) 0.29 | 0.26 |
| S-TG mm/L | 0.87 (0.39) | 0.94 (0.38) | 0.99 (0.42) | 0.95 (0.38) | 0.05 (-0.07; 0.18) 0.39 | 0.21 |
| Disease activity | | | | | | |
| DAS-28 | 2.0 (0.90) | 1.9 (0.84) | 2.0 (1.18) | 2.3 (1.33) | -0.27 (-0.7; 0.1) 0.15 | 0.35 |
| ESR | 10.8 (12.0) | 11.8 (10.9) | 11.7 (10.1) | 13.5 (11.4) | -0.76 (-3.57; 2.1) 0.62 | 0.13 |
| CRP | 2.2 (3.27) | 2.5 (3.84) | 2.3 (3.07) | 2.8 (3.33) | -0.15 (-1.66; 1.33) 0.87 | 0.05 |
| VAS-Global, 0-100 | 21.1 (20.0) | 16.6 (16.7) | 18.5 (19.0) | 29.5 (26.9) | -16.20 (-26.30; -6.40) 0.0015 | 0.77 |
| VAS-Pain, 0-100 | 19.9 (18.6) | 17.4 (16.8) | 20.1 (20.1) | 21.6 (22.4) | -5.16 (-15.0; 4.48) 0.30 | 0.25 |

Values are shown as mean and SD unless indicating otherwise. VO2mL/min, maximal oxygen uptake; O2-puls, oxygen pulse, VEmax, ventilatory maximal; RER; respiratory exchange ratio; HRmax, maximal heart rate; BP, blood pressure at rest; One-minute STS, One-minute Sit-To-Stand test; BMI, body mass index; WCF, waist circumference; Serum levels of S-TG, total cholesterol; S-HDL, high-density lipoprotein; S-LDL, low-density lipoprotein,; S-TC, triglycerides; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; CRP, C reactive protein. Missing values at month 3 in the CG, CRF (n=8), BP (n=6), grip strength (n=6), STS (n=6), Serum lipids (n=6), Anthropometry (n=6), DAS28 (n=7), ESR and CRP (n=6).

Table 6. Changes in secondary key outcomes from baseline to 3 months follow-up between the groups for the women and men separately

| | Intervention group | | Control group | | Between group | |
|---|---|---|---|---|---|---|
| | BL<br>Means (SD) | 3 Month<br>Means (SD) | BL<br>Means (SD) | 3 Month<br>Means (SD) | Mean diff of change BL to 3 Month<br>(95% CI)<br>*p*-value | Effect size |
| **Women** | (n=37) | (n=36) | (n=36) | (n=30) | | |
| $VO_2$max, mL/kg/min | 25.7 (5.4) | 28.1 (6.3) | 25.0 (5.7) | 24.3 (5.4)<br>(n=27) | 2.37 (1.14; 3.60)<br>0.0002 | 1.00 |
| Grip strength, N | 202.7 (60.4) | 227.8 (67.7) | 197.2 (62.4) | 185.1 (58.1) | 35.30 (15.20; 55.50)<br>0.0006 | 0.85 |
| One-minute STS, no | 23.5 (5.1) | 30.1 (5.2) | 24.8 (6.3) | 25.3 (6.3) | 5.27 (3.47; 7.06)<br><0.001 | 1.45 |
| DAS28 | 2.2 (0.83) | 2.1 (0.70) | 2.1 (1.25) | 2.5 (1.36) | -0.36 (-0.77; 0.04)<br>0.08 | 0.44 |
| **Men** | (n=6) | (n=5) | (n=8) | (n=8) | | |
| $VO_2$max, mL/kg/min | 29.3 (4.0) | 36.5 (5.0) | 33.1 (6.2) | 30.3 (5.5) | 9.48 (5.65; 17.06)<br>0.0016 | 1.57 |
| Grip strength, N | 287.8 (132.3) | 408.2 (67.6) | 284.5 (142.7) | 335.9 (105.9) | 25.2 (-89.0; 118.3)<br>0.65 | 0.26 |
| One-minute STS, no | 24.5 (7.9) | 32.2 (5.8) | 25.9 (7.3) | 28.3 (8.0) | 4.23 (-2.50; 11.00)<br>0.18 | 0.82 |
| DAS28 | 1.0 (0.76) | 0.9 (0.92) | 1.6 (0.61) | 1.4 (0.75) | 0.17 (-0.40; 0.76)<br>0.51 | 0.36 |

Values are shown as mean and SD unless indicating otherwise. $VO_2$max, weight corrected maximal oxygen uptake; One-minute STS, One-minute Sit-To-Stand test; DAS28, Disease Activity Score in 28 joints

# Expected benefit of high-intensity interval aerobic exercise program of 3 months for patients with RA: Improve cardiopulmonary function and health. Prevent deterioration in cardiovascular health and quality of life.

**Rheumatoid arthritis** (RA) is a chronic inflammatory disease with 0.7% prevalence rate in Sweden. RA is characterized by symmetrical inflammation of peripheral joints, although larger joints can also be affected. Clinical symptoms of RA are pain, stiffness, fatigue, limited range of motion in joints, and reduced muscle strength. Patients with RA have increased prevalence rates of comorbidities, mainly cardiovascular diseases and atherosclerosis. Despite more effective control of inflammation by improved pharmacological therapies, reduced physical function, cardiovascular disease and increased arterial stiffness remain major problems in RA.

**Cardiovascular disease.** Patients with RA have markedly increased risk for cardiovascular disease, leading to increased mortality[1]. Increased mortality in RA has partially been attributed to cardiac insufficiency and myocardial infarction[1, 2]. Cardiopulmonary and respiratory functions are assessed by means of cardiopulmonary exercise test (CPET). A low maximum oxygen uptake (VO2max) has been suggested a stronger risk factor for cardiovascular disease and mortality than high blood pressure, overweight, smoking, and hyperlipidemia[3].

Patients with RA have lower cardiopulmonary fitness, with a reduction of 20% in VO2max compared to age-matched healthy controls[4]. There can be several reasons for the low VO2max in patients with RA, for example, cardiovascular effects of the inflammatory process. However, a probable reason is low physical activity level of patients with RA. The general recommendation for health-enhancing physical activity is: activity/exercise corresponding to a moderate intensity for ≥150 minutes/week or activity/exercise at vigorous intensity for ≥75 minutes/week[5]. Only 36% of RA patients report physical activity at these levels[6]. Indeed, regular physical activity is a common problem, as only a minority of the Swedish population successfully follow recommendations, when objectively assessed using an accelerometer[7].

**Atherosclerosis** and arterial stiffness are commonly observed in RA [8] and are associated with increased risk of cardiovascular disease. Atherosclerosis in RA is linked to the inflammation driving the rheumatoid disease along with general risk factors, such as low physical activity level, high body mass index (BMI), hypertension and smoking. The gold standard measurement of stiffness in larger arteries is the aortic pulse wave velocity (PWV). Pulse wave velocity increases with age, even in the absence of clinical disease. Studies indicate that aerobic exercise diminishes arterial stiffness[9].

**Metabolic and inflammation profiles.** RA is characterized by chronic inflammation, with increased production of pro-inflammatory cytokines. Adipokines are metabolic and inflammatory factors that are released in adipose tissue. A well-characterized adipokine is leptin, which is associated with disease activity in RA. Reduction of risk in cardiovascular disease through physical activity has been associated with improved inflammatory and lipid profiles and improved insulin resistance. Changes in these metabolic and inflammatory factors will be examined.

**Cardiorespiratory exercise.** Regular physical activity and exercise have been shown to confer multiple health effects and to decrease mortality from cardiovascular diseases, stroke, cancer and diabetes. Therefore, the general guidelines related to physical activity for healthy people are currently also recommended for patients with rheumatic diseases [10] and physically active people with risk of clinical coronary artery disease[11].

**High-intensity interval aerobic exercise.** Physical activity is any bodily movement that increases energy expenditure, while exercise is structured and planned physical activity.

Moderate-intensity aerobic exercise is defined as achieving 60%–74% of the maximum heart rate, while high-intensity level is 75%–94% of the maximum heart rate. High-intensity interval exercise is a relatively new mode of exercise, with alternating short intervals of high and low intensity exercise. The target heart rate during the high-intensity bouts is 90%–95% of the maximum heart rate[12]. This exercise mode has attracted intense interest from the healthy population and among patients with different diseases. One reason for this is that high-intensity exercise is time-efficient and results in a greater improvement in VO2max than moderate continuous exercise[13]. This is important when aiming to prevent cardiovascular disease, since the risks for cardiovascular morbidity and mortality decrease for every increment in 1 ml of VO2max[14].

Exercise interventions for patients with RA are commonly conducted at low or moderate intensities[10], while studies of high-intensity aerobic exercise in RA are scarce. However, a small sample (N=12) with younger (mean age, 33 years) patients with either juvenile RA or RA showed tolerance to high-intensity exercise[15], although no firm conclusions could be drawn.

**Our previous studies** Our long-term goal is to improve cardiopulmonary function and health for patients with rheumatic disease. The proposed project is based on our previous research on physical activity/ exercise in general [7, 11, 14, 16] and in patients with rheumatic diseases in particular[17-19]. We showed that patients with axial spondyloarthritis (axSpA) can manage aerobic exercise at high intensity[18]. VO2max and disease activity scores [18] as well as fatigue, sleep and mood were improved in the patients with axSpA as a result of the high-intensity exercise[20]. All of these benefits are of major importance to cope with rheumatic disease in daily living. The patients reported increased physical activity at a moderate-to-high intensity level at the 1-year follow-up[19], showing that they motivated for long-term exercise, which is an important outcome. Therefore, we deem it important to study the effects and feasibility of high-intensity interval exercise also for patients with RA.

A pilot study (n=4) was conducted, and it showed positive response of patients with RA engaged in in HIIT program. All patients managed the high intensity exercise level. As patients with RA have an increased risk of cardiovascular disease, and exercise at a high intensity can involve greater risks[11, 16], their risk profile will be taken to account. We will examine the patients using the European Sport Cardiology algorithm, designed for risk evaluation of patients with risk of cardiovascular disease[11]. Pedagogic modes, such as person-centered guidance [17] and motivational support[18, 19], which have previously been shown to contribute to successful outcomes, will be applied in the planned study.

**The overarching objective of this study** is to evaluate the effects of high-intensity interval aerobic training (HIIT) and strength exercise on cardiovascular health, physical fitness and general health for patients with RA who are receiving the standard of care.

**We hypothesize** that a 12-week high-intensity interval exercise program will provide substantial improvements in the cardiovascular health, physical fitness and general health of patients with rheumatoid arthritis (RA).

**Study design.** A randomized controlled intervention trial (0–12 weeks).

**Patients**

**Criteria for inclusion.** Patients with established RA diagnosed according to ACR/EULAR 1987/2010 criteria, which comprise clinical examinations of joints, radiological and laboratory measurements. Disease duration >1 year, age range 20–60 years, stable medication on anti-rheumatic drugs for >3 months, and low-to-moderate disease activity (<5.1) according to the Disease activity score 28 (DAS28).

**Criteria for exclusion.** To cater for the safety of patients participating in this study, it is necessary to exclude patients with other severe diseases that may be associated with adverse events or restrict participation in high-intensity exercise, such as cerebrovascular diseases,

diabetes, severe hypertension, chronic obstructive pulmonary disease, and other severe pulmonary diseases[11, 16]. Screening for exclusion criteria is conducted in several phases of the examination, and include electrocardiogram, CPET, and pulse wave velocity test. Other exclusion criteria are arthroplasty of large joints, inability to manage exercise test (CPET), pregnancy, already participating in regular aerobic or strength exercise at high intensity for >1 hour/ week during the last 6 months, inability to speak or read Swedish.

**Procedure**

**Recruitment**. In total, 88 patients (see power calculation) with established RA will be recruited from the rheumatology units at Sahlgrenska University Hospital in Gothenburg and Mölndal, Uddevalla Hospital through the Swedish Rheumatology Quality Register (SRQ).

Oral (by telephone) and written information about the study will be presented to potential participants. Screening will involve assessment of inclusion and exclusion criteria for each subject, according to previously established screening protocol for risk factors of cardiovascular diseases before participation in sports or intense exercise[11, 16]. Those fulfilling criteria will be invited to Clinical Rheumatology Research unit at Sahlgrenska University Hospital. Information about age, gender, disease duration, and pharmacologic treatments will be gathered through structured interviews, medical records and SRQ.

Clinical examinations by a rheumatologist will comprise the general health status and evaluations of rheumatoid disease and comorbidities. Blood samples will be taken, and an electrocardiogram (ECG) will be conducted. A physical assessment with submaximal bicycle test and muscle function will be conducted to determine if the patient can manage the maximal CPET. Patients will be asked to fill in a battery of questionnaires. Thereafter, patients will be referred for the CPET of VO2max and the PWV test for screening for risk of adverse events.

**Statistics.** To achieve 80% power to detect 10% difference in change between the groups in VO2max, a total of 77 participants needs to be recruited. The calculation of baseline (34 ml/min and SD of difference: 5.0) is based on a previous study (Bilberg, Rheumatol 2005). A total of 88 patients will be recruited to compensate for 20% dropouts. Within- and between-group differences will be analyzed by parametric statistics. If major deviations within the normal range are detected, we will consider data transformation or non-parametric statistics. A statistical advisor will be consulted for all the analyses.

**Randomization** will be conducted in blocks of four subjects by a computer-generated sequence prepared by a statistician. Concealed, sequentially numbered, sealed, opaque envelopes will be opened by a person not involved in the examinations or treatments, who will also inform regarding the group to which the participant is allocated.

**Control group** (0-12 weeks)

Participants in the control group meet a physiotherapist for one session to introduce the general health recommendations for physical activity [5] and encourage physical activity on moderate intensive level ≥150 minutes/week. Participants are introduced to a home exercise program for improvement of muscle function and balance during the intervention period [5, 17]. Verbal and written instructions are given, according to previous used model[17].

**Intervention** (0-12 weeks)

The program includes 12 weeks of aerobic and resistance exercises. Two sessions/week are supervised by an experienced physiotherapist, while a third additional session is non-supervised session of the patient´s own choice. The target of the HIIT intervals is 90%–95% of maximum heart rate (13), based on measured maximum heart rate obtained during CPET at baseline. The high-intensity intervals are alternated with recovery phases at 70% of max heart rate. The exercise protocol comprises 10 minutes of warm-up, followed by 25 minutes of exercise, comprising 4 intervals of 4-minute bouts of high-intensity exercise and 3 intervals of 3-minute bouts of active recovery. The session ends with cooling down for 3–5 minutes.

The exercise is initiated with an individual session, at moderate exercise intensity, progressing to high intensity according to individual capacity. Exercise sessions are modified according to present health at the time of the session (actual symptoms, lack of energy, stress, etc.). Exercise guidance follows principles of self-efficacy and person-centeredness, applying supervision, identification of possible limitations and barriers, exercise diary, a portable heart rate monitor, and continuous dialogue with individual feed-back by a physiotherapist.

Thus, the exercise program is continuously monitored, adapted to each participant and conducted with rigorous guidance, whereby a physiotherapist follows each patient´s heart rate, symptoms, and perceptions. An individual heart rate sensor (Polar H10) connected to a training application loaded in the patient´s cellphone (Polar Beat) and used at each exercise session for monitoring heart rate. Two physiotherapists trained in cardiopulmonary resuscitation (CPR) are present at each session for safety reasons. A mobile intensive care group from the intensive care unit is available less than 5 minutes away from the exercise facilities at the hospitals. Resistance exercise sessions of 20 minutes each include large muscle groups in lower and upper extremities and trunk: 8–10 repetitions with 2–3 sets, with or without equipment.

**Primary outcome**

*Cardiopulmonary function* (0 -12 weeks) is assessed by weight adjusted VO2max (ml/kg/min), obtained during progressively increasing work on a bicycle, during which gas exchange will be analyzed, called the cardiopulmonary exercise test (CPET)**.** Registration of ECG data, heart rate and blood pressure will be conducted. A well-established clinical protocol will be applied, and this test is the gold standard when measuring improvement in physical capacity and is directly related to cardiovascular function. The test will be performed in the SU/Clinical Physiology laboratory, as a previous exercise study, for safety reasons and as an outcome measure [17].

**Secondary outcomes**

*Metabolic factors* (0-12 week). Lipid status is assessed by changes in blood levels of triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol. Blood samples are drawn after eight hours of fasting.
*Physical function* (0-12 week). Muscle function will be assessed using the 1-minute Sit-to-Stand test and using a dynamometer to measure the grip strength of the hand. Both tests are reliable and have been validated for patients with RA.
*Anthropometry measurements* (0-12 weeks) will be assessed with body weight and body height, BMI-score (kg/m2) and waist circumference.
*Resting blood pressure* is recorded with an ambulatory blood pressure monitor with the patient in a seated position, where the lowest value out of two was recorded.
*Disease activity* (0-12 week) measured using DAS28, a gold standard in rheumatology, based on clinical assessment of 28 joints (swollen, tender), patients´ rating of health (VAS), and sedimentation rate (ESR). A score <5.1 indicates low-to-moderate disease activity and <2.6 indicate remission.
Patient-administered questionnaires on health, symptoms and physical activity are well-established, reliable and valid instruments for patients with RA, and they have been applied in our previous studies.
*Pain and global health* (0-12 week) are rated on a Visual Analogue Scale (VAS).
*Physical activity* (0-12 week) is reported on a standardized questionnaire, called the Leisure Time Physical Activity instrument (LTPAI).
*Changes in symptoms* (12-week) is assessed with the patient global impression of change (PGIC) questionnaires.
*Feasibility* has previously been evaluated as adherence to the exercise protocol [10]. In this study, will document: all the reasons for declining to participate and for exclusions during the screening process, attendance at exercise sessions; adherence to the study protocol (maximum heart rate, average heart rate); and possible adverse effects.

**Ethics**

Rigorous control of safety is applied during the screening process as well as when planning and

leading the exercise. Integrity of patients is protected by coding and anonymizing the data. An application to the National Ethics Committee in Sweden will be submitted for approval of the study plan. Data Protection Office at SU will be contacted for GDPR. Incidental findings with regard to cardiovascular health will be remitted to the Cardiology clinic by JB. Other unexpected findings related to the subjects´ health will be addressed by JB who will contact the relevant specialist clinic or general practitioner. JB will contact the Rheumatology clinic of the patient regarding unexpected findings relating to the patient's rheumatic disease.

**Research environment and Research facilities relevant to the project**
The research team combines three units at the University of Gothenburg (GU), The Sahlgrenska Academy: 1) Institute of Neuroscience and Physiology, Section of Health and Rehabilitation (KM, AB); 2) Institute of Medicine, Department of Molecular and Clinical Medicine (SS, MB); and 3) Institute of Medicine, Department of Rheumatology and Inflammation Research (JB). The clinical units are Rheumatology/SU, Physiotherapy/SU and Rheumatology/Uddevalla.

*Coordination.* The recruitment will be conducted by Annelie Bilberg and Jan Bjersing together, with tight weekly cooperation. AB will coordinate the examinations and the treatments both for the intervention- and control group. Site visits will be conducted, and telephone meetings will be held each or each other week.

*Clinical environment.* Patients will be recruited from rheumatology units at Sahlgrenska University Hospital (SU), and from Uddevalla hospitals. Clinical examinations are conducted at the Clinical Research Facility (CRF) in SU/Rheumatology (JB, AB), and at SU/ Clinical physiology laboratory (SS). Exercise interventions are to be conducted at physiotherapy units at SU and Uddevalla hospitals, by using exercise equipment required at these facilities All the physiotherapists will receive appropriate training and education before the start of the project by the project leader (AB).

**Personal resources, competence and role in the project**
**Annelie Bilberg (AB),** Senior Physiotherapist, PhD. Working clinically as a physiotherapist at the rheumatology unit, Sahlgrenska University Hospital, Gothenburg and affiliated to Institute of Neuroscience and Physiology/ Physiotherapy. Coordinator for physiotherapists within rheumatology in the Western region of Sweden, which will facilitate coordination of this study, and long-term implementation of the exercise program in clinic. Clinical expert in exercise and rheumatic disease. Project leader and coordinator of the present study, with responsibility for recruiting the patients, as well as the clinical examinations and coordination of all the examinations and treatments for the participants in the study. She will educate and support the physiotherapists acting as leaders at the three study sites in the Western region of Sweden.
**Jan Bjersing (JB)**, MD PhD, Associate Professor and specialist in rheumatology. JB is employed at SU/Rheumatology, including a 20% adjunct lectureship at GU, The Sahlgrenska Academy. Will be responsible for the recruitment and screening of patients. He has experience from several clinical studies involving studies of biomarkers during exercise.
**Kaisa Mannerkorpi (KM)**, PhD and Professor in physiotherapy at the Institute of Neuroscience and Physiology, Section of Health and Rehabilitation, Unit of Physiotherapy. She has supervised seven previous exercise studies. Expert in personal centered health. She is responsible for the personal centered support for long-term exercise after end of the supervised HIIT in the intervention group.
**Sara Svedlund (SS)**, Care unit Chief Physician, MD, PhD, Associate Professor at the Department of Clinical Physiology/SU, and Institute of Medicine, Department of Molecular and Clinical Medicine. Responsible for the execution, interpretation and analysis of the CPET and PWV data in this study. Runs an academic core laboratory that uses different modalities for cardiovascular characterization.
**Mats Börjesson (MB),** Professor of Sports Physiology and MD, Specialist in Cardiology and Internal medicine. Special research interest in health benefits and potential risks of physical activity and sports (Sports Cardiology). Head of Center for Health and Performance Laboratory at University of Gothenburg, Sweden. He is responsible for the research design

from a cardiological perspective including safety aspects and participates in the analysis of the data.

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Table 4. Exploratory interaction analysis on $VO_2$max for the total study population (N=87) and baseline variables

| | Interaction *p*-value | Mean diff of change (95%CI) | *p*-value |
|---|---|---|---|
| Age | 0.3948 | | |
| Gender | 0.0005 | | |
| Female | | 2.36 (1.13; 3.59) | 0.0003 |
| Male | | 9.67 (4.25; 15.09) | 0.0003 |
| Weight, kg | 0.048 | | |
| ≤70 | | 2.72 (0.82; 4.63) | 0.0069 |
| >70 | | 4.35 (1.91; 6.80) | 0.0008 |
| Length, cm | 0.0002 | | |
| ≤170 | | 1.72 (-0.01; 3.45) | 0.0510 |
| >170 | | 5.74 (3.44; 8.04) | <.0001 |

Interaction analyses between the total study population and baseline variables regarding primary efficacy variable as dependent

Table 5. The per procol analyses for the changes in secondary outcomes from baseline to 3 months follow-up between the groups

| | Intervention group (n=33) | | Control group (n=44) | | Between group | |
|---|---|---|---|---|---|---|
| | BL<br>Means (SD) | 3 Month<br>Means (SD) | BL<br>Means (SD) | 3 Month<br>Means (SD) | Mean diff of change BL to 3M<br>(95% CI)<br>*p*-value | Effect size |
| VO2 mL/min | 2108 (450.0) | 2378 (581.0) | 2013 (569.0) | 1988 (579.0) | 292.1 (195.6; 389.9)<br><0.0001 | 1.45 |
| O2-pulse mL/beat/min | 12.2 (2.6) | 13.9 (3.5) | 11.9 (3.1) | 12.1 (3.4) | 1.61 (1.05; 2.17)<br><0.0001 | 1.39 |
| VEmax L/min | 87.6 (19.3) | 93.5 (22.3) | 82.1 (22.2) | 81.2 (24.9) | 7.21 (1.2; 13.21)<br>0.016 | 0.57 |
| RER | 1.18 (0.08) | 1.15 (0.09) | 1.20 (0.09) | 1.20 (0.10) | -0.016 (-0.04; 0.01)<br>0.018 | 0.59 |
| HRmax, beats/min | 173.9 (11.1) | 171.9 (11.9) | 169.4 (16.5) | 164.8 (16.3) | 0.87 (-2.82; 4.45)<br>0.65 | 0.12 |
| Systolic BP | 124.0 (17.6) | 121.2 (16.4) | 123.9 (15.9) | 124.4 (17.7) | -2.39 (-8.23; 3.47)<br>0.43 | 0.19 |
| Diastolic BP | 74.9 (11.6) | 73.5 (10.3) | 74.5 (10.5) | 75.4 (11.3) | -1.72 (-5.03; 1.58)<br>0.31 | 0.25 |
| Grip strength, N | 228.2 (79.4) | 262.4 (90.7) | 213.1 (87.4) | 216.8 (93.0) | 32.2 (5.2; 58.9)<br>0.02 | 0.56 |
| One-minute STS, no | 25.0 (5.4) | 30.7 (5.1) | 25.0 (6.4) | 25.9 (6.7) | 4.28 (2.60; 5.94)<br><0.0001 | 1.20 |
| Anthropometry | | | | | | |
| Weight, kg | 80.0 (16.5) | 79.5 (15.5) | 78.5 (19.1) | 78.2 (19.2) | -0.55 (-1.47; 0.39)<br>0.24 | 0.28 |
| BMI, kg/m2 | 27.2 (5.8) | 27.0 (5.5) | 27.1 (5.3) | 26.9 (5.1) | -0.17 (-0.48; 0.15)<br>0.29 | 0.26 |
| Waist circumference, cm | 90.9 (14.7) | 87.1 (12.2) | 89.1 (15.2) | 88.7 (14.4) | -3.56 (-6.16; -0.94)<br>0.0098 | 0.64 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Serum lipids | | | | | | |
| S-TC | 5.34 (1.43) | 5.19 (1.41) | 5.16 (1.00) | 5.22 (0.95) | -0.15 (-0.39; 0.08) 0.2 | 0.31 |
| S-HDL | 1.62 (0.41) | 1.61 (0.36) | 1.58 (0.39) | 1.59 (0.39) | -0.02 (-0.11; 0.08) 0.71 | 0.09 |
| S-LDLmm/L | 3.64 (1.26) | 3.45 (1.26) | 3.45 (0.89) | 3.47 (0.78) | -0.11 (-0.31; 0.1) 0.29 | 0.26 |
| S-TG mm/L | 0.87 (0.39) | 0.94 (0.38) | 0.99 (0.42) | 0.95 (0.38) | 0.05 (-0.07; 0.18) 0.39 | 0.21 |
| Disease activity | | | | | | |
| DAS-28 | 2.0 (0.90) | 1.9 (0.84) | 2.0 (1.18) | 2.3 (1.33) | -0.27 (-0.7; 0.1) 0.15 | 0.35 |
| ESR | 10.8 (12.0) | 11.8 (10.9) | 11.7 (10.1) | 13.5 (11.4) | -0.76 (-3.57; 2.1) 0.62 | 0.13 |
| CRP | 2.2 (3.27) | 2.5 (3.84) | 2.3 (3.07) | 2.8 (3.33) | -0.15 (-1.66; 1.33) 0.87 | 0.05 |
| VAS-Global, 0-100 | 21.1 (20.0) | 16.6 (16.7) | 18.5 (19.0) | 29.5 (26.9) | -16.20 (-26.30; -6.40) 0.0015 | 0.77 |
| VAS-Pain, 0-100 | 19.9 (18.6) | 17.4 (16.8) | 20.1 (20.1) | 21.6 (22.4) | -5.16 (-15.0; 4.48) 0.30 | 0.25 |

Values are shown as mean and SD unless indicating otherwise. VO2mL/min, maximal oxygen uptake; O2-puls, oxygen pulse, VEmax, ventilatory maximal; RER; respiratory exchange ratio; HRmax, maximal heart rate; BP, blood pressure at rest; One-minute STS, One-minute Sit-To-Stand test; BMI, body mass index; WCF, waist circumference; Serum levels of S-TG, total cholesterol; S-HDL, high-density lipoprotein; S-LDL, low-density lipoprotein,; S-TC, triglycerides; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; CRP, C reactive protein. Missing values at month 3 in the CG, CRF (n=8), BP (n=6), grip strength (n=6), STS (n=6), Serum lipids (n=6), Anthropometry (n=6), DAS28 (n=7), ESR and CRP (n=6).

Table 6. Changes in secondary key outcomes from baseline to 3 months follow-up between the groups for the women and men separately

| | Intervention group | | Control group | | Between group | |
|---|---|---|---|---|---|---|
| | BL<br>Means (SD) | 3 Month<br>Means (SD) | BL<br>Means (SD) | 3 Month<br>Means (SD) | Mean diff of change BL to 3 Month<br>(95% CI)<br>*p*-value | Effect size |
| **Women** | (n=37) | (n=36) | (n=36) | (n=30) | | |
| $VO_2$max, mL/kg/min | 25.7 (5.4) | 28.1 (6.3) | 25.0 (5.7) | 24.3 (5.4)<br>(n=27) | 2.37 (1.14; 3.60)<br>0.0002 | 1.00 |
| Grip strength, N | 202.7 (60.4) | 227.8 (67.7) | 197.2 (62.4) | 185.1 (58.1) | 35.30 (15.20; 55.50)<br>0.0006 | 0.85 |
| One-minute STS, no | 23.5 (5.1) | 30.1 (5.2) | 24.8 (6.3) | 25.3 (6.3) | 5.27 (3.47; 7.06)<br><0.001 | 1.45 |
| DAS28 | 2.2 (0.83) | 2.1 (0.70) | 2.1 (1.25) | 2.5 (1.36) | -0.36 (-0.77; 0.04)<br>0.08 | 0.44 |
| **Men** | (n=6) | (n=5) | (n=8) | (n=8) | | |
| $VO_2$max, mL/kg/min | 29.3 (4.0) | 36.5 (5.0) | 33.1 (6.2) | 30.3 (5.5) | 9.48 (5.65; 17.06)<br>0.0016 | 1.57 |
| Grip strength, N | 287.8 (132.3) | 408.2 (67.6) | 284.5 (142.7) | 335.9 (105.9) | 25.2 (-89.0; 118.3)<br>0.65 | 0.26 |
| One-minute STS, no | 24.5 (7.9) | 32.2 (5.8) | 25.9 (7.3) | 28.3 (8.0) | 4.23 (-2.50; 11.00)<br>0.18 | 0.82 |
| DAS28 | 1.0 (0.76) | 0.9 (0.92) | 1.6 (0.61) | 1.4 (0.75) | 0.17 (-0.40; 0.76)<br>0.51 | 0.36 |

Values are shown as mean and SD unless indicating otherwise. $VO_2$max, weight corrected maximal oxygen uptake; One-minute STS, One-minute Sit-To-Stand test; DAS28, Disease Activity Score in 28 joints