

ORIGINAL RESEARCH

Effect of high-intensity interval training in physiotherapy primary care for patients with inflammatory arthritis: the ExeHeart randomised controlled trial

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ABSTRACT

Objectives To assess the effect of high-intensity interval training (HIIT) delivered in physiotherapy primary care on the primary outcome of cardiorespiratory fitness (CRF) in patients with inflammatory arthritis (IA). Additionally, to explore the effects of HIIT on secondary outcomes, including cardiovascular disease (CVD) risk factors and disease activity.

Methods Single-blinded randomised controlled trial with 60 patients randomly assigned to either a control group receiving usual care or an exercise group receiving usual care and 12 weeks of individualised HIIT at 90%–95% peak heart rate. Outcomes were assessed at baseline, 3 months and 6 months post baseline and included CRF measured as peak oxygen uptake (VO_{2peak}), classic CVD risk factors, disease activity, anthropometry and patient-reported physical activity, pain, fatigue, disease impact and exercise beliefs and self-efficacy.

Results Intention-to-treat analysis demonstrated a significant between-group difference in VO_{2peak} at 3 months (2.5 mL/kg/min, 95% CI 0.9 to 4.0) and 6 months (2.6 mL/kg/min, 95% CI 0.8 to 4.3) in favour of the exercise group. A beneficial change in self-reported physical activity in favour of the exercise group was observed at 3 and 6 months. The HIIT intervention was well-tolerated with minimal adverse events and no apparent impact on disease activity. Differences in secondary outcomes related to CVD risk factors, disease impact, pain, fatigue and exercise beliefs and self-efficacy were generally small and non-significant.

Conclusion After 12 weeks of supervised HIIT delivered in physiotherapy primary care, patients with IA demonstrated a favourable improvement in CRF, with sustained effects at 6-month follow-up.

Trial registration number NCT04922840.

INTRODUCTION

Inflammatory arthritis (IA), including rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA), are autoimmune

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ High-intensity interval training (HIIT) is known to enhance both cardiorespiratory fitness (CRF) and cardiovascular health, but its effectiveness as an intervention for patients with inflammatory arthritis (IA) in physiotherapy primary care is unknown.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that HIIT delivered in physiotherapy primary care for patients with IA can lead to a sustained increase in CRF without any adverse effects on disease activity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study support the implementation of HIIT in physiotherapy primary care as a way to increase CRF in patients with IA.

diseases characterised by joint inflammation, pain, fatigue and extra-articular manifestations. Patients with IA have an elevated risk of cardiovascular disease (CVD) driven by the proatherogenic effects of systemic inflammation on the vasculature, as well as a high prevalence of traditional CVD risk factors such as smoking, hypertension, adiposity and hypercholesterolemia.^{1–3} In addition to screening of traditional CVD risk factors, class 1a level evidence promotes habitual physical activity to optimise CVD risk management.⁴ Physical activity is of major influence to cardiorespiratory fitness (CRF), a renowned and clinically important measure of how well the body delivers oxygen to working muscles.^{5,6} CRF is an independent and modifiable risk factor of CVD,⁶ and modest increases in CRF associate with increased longevity and lower risk of cardiovascular events.^{7,8}

Exercise-induced adaptations in CRF are dose-dependent, and high-intensity interval training (HIIT) has been shown to elicit superior improvements in CRF compared with exercise at lower intensities.^{9–10} Empirical data further indicate favourable effects of HIIT on CVD risk factors related to haemodynamics, lipid parameters and body composition.^{11–13} Nonetheless, the sustainability of HIIT as a long-term exercise mode has been questioned.¹⁴

There is growing support for the use of exercise to downregulate inflammatory pathways and alleviate symptom burden in IA.^{15–16} However, physical activity levels and CRF are reportedly lower in patients with IA compared with the general population,^{17–18} and patients with IA call for individualised exercise programmes tailored by health professionals.¹⁹ Despite awareness of increased CVD risk in IA and the beneficial effects of exercise on both CRF and disease activity, tailored exercise remains to be integrated in the cluster of CVD risk factors commonly addressed in IA care.²⁰ Evidence on the effect of HIIT for patients with IA is derived from clinical trials that primarily focused on the effect of HIIT on disease activity.^{21–22} There is currently a limited number of studies designed to assess the cardioprotective effects of HIIT for patients with IA,²³ as well as a lack of studies that evaluate the effect of HIIT delivered outside specialised healthcare settings.

Therefore, the primary purpose of the ExeHeart randomised controlled trial (RCT) was to report on the effect of a 12-week HIIT intervention set in physiotherapy primary care on CRF in patients with IA. Additionally, we aimed to explore the impact of HIIT on classic CVD risk factors and disease activity in patients with IA, potential benefits of HIIT beyond the primary endpoint, and to assess safety of the HIIT intervention.

METHODS

Trial design

The ExeHeart study is an assessor-blinded, RCT comparing the effects of 12-week HIIT supervised by physiotherapists in primary care with usual care (control group) in a 1:1 ratio. The trial was prospectively registered (NCT04922840). A comprehensive study protocol has been previously published²⁴ and is outlined below. Reporting is guided by Consolidated Standards of Reporting Trials statement for randomised trials of non-pharmacologic treatments,²⁵ Consensus on Exercise Reporting Template²⁶ and the Position Statement on Exercise Dosage in Rheumatic and Musculoskeletal Diseases (IMPACT-RMD toolkit).²⁷

Participants

Patients meeting the eligibility criteria (table 1) were recruited from the Preventive Cardio-Rheuma Clinic at Diakonhjemmet Hospital, Oslo, Norway. Study enrolment was initiated in August 2021 and follow-up was completed *primo* March 2023.

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
18–70 years old	Lower extremity injury or surgery ≤12 months
Rheumatologist-verified IA diagnosis: RA, SpA or PsA	Cognitive disability
BMI: 18.5–40 kg/m ²	Primary neurological disease
Ability to walk unaided for ≥15 min	Participation in HIIT ≥1/week in the past 3 months leading up to study inclusion
Norwegian and/or English speaking	Contraindication to maximal exercise test as defined by ACSM ²⁹

ACSM, American College of Sports Medicine; BMI, body mass index; HIIT, high-intensity interval training; IA, inflammatory arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

Intervention

Regardless of group allocation, all patients received usual care at the Preventive Cardio-Rheuma Clinic, including CVD risk assessment, general lifestyle advice and relevant CVD medication. Between baseline and the 3-month follow-up, patients assigned to the intervention group were given a 12-week exercise programme, each week consisting of two face-to-face supervised HIIT sessions and one self-guided exercise session at moderate intensity. The first 2 weeks focused on a gradual increase in exercise load and familiarisation with the protocol. Exercise intensity was monitored by heart rate monitors and rating of perceived exertion (RPE) by the Borg 6–20 Scale.²⁸ HIIT sessions were singly delivered and tailored to the following protocol: 10 min warm-up followed by 4×4 min high intensity exercise at 90%–95% of peak heart rate (HR_{peak}), RPE 16–18, interspersed by 2–3 min active recovery at 60%–70% HR_{peak} , RPE 11–13. Patients were recommended to use uphill walking or running, but other options such as cycling, rowing, and elliptical machines were also acceptable. Workload was individually adapted to ensure exercise intensity aligned with the prescribed HIIT protocol. Throughout the intervention period, absolute intensity was continuously adjusted to achieve the targeted relative intensity. Patients were also advised to perform a third weekly non-supervised exercise session at moderate intensity, consisting of a 10 min warm-up followed by 30 min at RPE 12–14.

Four physiotherapists employed at three primary care clinics in Oslo, Norway, supervised the HIIT exercise sessions and advised patients on how to perform the third weekly, self-guided exercise session. While the physiotherapists were seasoned practitioners, they had limited prior experience with HIIT as a treatment modality and were not specialised in rheumatology. Prior to the study, they received educational sessions on how to prescribe and monitor the exercise protocol and were provided with treatment manuals and clinical checklists to use during

HIIT sessions. Unblinded study personnel were available for on-demand consultation of any clinical issues that arose during the intervention period.

After the study ended, control group participants were provided with a fitness watch and a single HIIT session tailored by a physiotherapist from the Norwegian National Unit for Rehabilitation for Rheumatic Patients with Special Needs, Diakonhjemmet Hospital, Oslo, Norway.

Outcome assessments

Outcomes were assessed at baseline, 3 months and 6 months post baseline and included questionnaires and clinical examinations. Medical background information regarding IA diagnosis and comorbidities were obtained from the patient's medical record. Assessors blinded to group allocation conducted all examinations in the following order: blood samples, waist circumference, height and body composition, resting heart rate, blood pressure and arterial stiffness, tender and swollen joint count (if applicable), resting ECG, spirometry and a cardiopulmonary exercise test (CPET). Measurements taken at follow-up timepoints were carried out at the same time of day as the baseline measurements.

Primary outcome measure and end criteria

The primary outcome was change in CRF 3 months post baseline. CRF was quantified as peak oxygen uptake (VO_{2peak}) in mL/kg/min by CPET. Respiratory gas exchange and ventilation were sampled over eight breaths and averaged over 30 s intervals. VO_{2peak} was defined as the highest 30 s VO_2 observed throughout the exercise test. A 12-lead ECG and percutaneous oxygen saturation were assessed continuously throughout the test, and blood pressure was measured every other minute. RPE was rated by Borg 0–10 Scale,²⁸ and blood lactate was sampled within 60 s of test termination. Peak oxygen pulse, a surrogate of left ventricular stroke volume, was indexed as peak VO_2 (mL/min) divided by HR_{peak} . To ensure validity of repeated CPETs and assess level of maximal exertion, commonly used end criteria were recorded, including respiratory exchange ratio, Borg RPE 0–10, HR_{peak} and postexercise blood lactate levels.^{29 30}

Secondary outcomes: clinical measures

Secondary outcome data included CRF as absolute capacity (L/min) and adjusted to fat-free mass (FFM). Non-fasting blood samples were collected according to current procedures at the hospital laboratory and analysed for C reactive protein (CRP), erythrocyte sedimentation rate (ESR), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides.

Waist circumference was recorded as the mean of two attempts and height was measured by stadiometer. Body weight, total FFM, total fat mass and visceral fat indicator

were measured by bioelectrical impedance analysis and body mass index was computed as height in cm/kg².

An ambulatory blood pressure monitor was used to measure systolic and diastolic blood pressure, mean arterial pressure, arterial stiffness (measured as pulse wave velocity and augmentation index) and resting heart rate. In the absence of statins and/or antihypertensives, Systemic Coronary Risk Estimation 2 (SCORE2) was estimated by the low-risk country algorithm,⁴ including a 1.5 multiplication factor for patients with RA.¹ An increased CVD risk was categorised as use of statins and/or anti-hypertensives or SCORE2 $\geq 2.5\%$, $\geq 5\%$ and $\geq 7.5\%$ for ages < 50 years, 50–69 years and ≥ 70 years, respectively.⁴

Disease activity was classified as remission, low, moderate or high using disease-specific composite instruments: Disease Activity Score-28 Calculator for RA, Ankylosing Spondylitis Disease Activity Score for SpA and Disease Activity Index for Psoriatic Arthritis for PsA.²⁴

Secondary outcomes: patient reported

Prior to all study visits, patients answered a digital questionnaire with the following items: demography, use of medication, healthcare services and cigarettes/snuff, pain and fatigue by Numerical Rating Scale 0–10 (0=best) and CVD history and symptoms. Exercise beliefs and exercise habits were indexed by 20 questions over four domains: exercise self-efficacy, barriers to exercise, benefits of exercise and impact of exercise on IA.³¹ Physical activity level was quantified by three questions regarding frequency, duration and intensity of habitual exercise.³² Self-reported burden of disease was evaluated according to IA entity: Rheumatoid Arthritis Impact of Disease for patients with RA, Bath Ankylosing Spondylitis Disease Activity Index for patients with SpA and Psoriatic Arthritis Impact of Disease for patients with PsA.²⁴

Registration of adherence and safety

HIIT exercise sessions were logged by the physiotherapist in the patient's personal training diaries and attendance was tallied as number of attended HIIT sessions over number of scheduled HIIT sessions. During HIIT sessions, heart rate and RPE 6–20 were recorded by the physiotherapist at the third minute of each interval bout. Patients self-recorded the moderate-intensity non-supervised exercise sessions and were instructed to register max and mean heart rate as well as overall RPE 6–20. Heart rate was further expressed as a percentage of the highest HR_{peak} recorded during CPET. Control group participants reported their exercise habits over the past 3 months retrospectively at 3-month follow-up, while all participants reported exercise habits retrospectively at 6-month follow-up. Measures of safety included absence of disease flares²⁴ and reports of adverse events.

Sample size

Sample size was determined based on the primary outcome: change in VO_{2peak} following the 12-week intervention. To detect an increase of 3.5 mL/kg/min in

VO_{2peak} , which has been associated with a significantly lower risk of CVD and all-cause mortality,^{8,33} a total of 60 patients was deemed adequate. This was calculated with allowance for a possible 20% dropout rate, a SD of 4.5 mL/kg/min,³⁴ a power of 0.8 and an alpha of 0.05. The secondary outcomes were considered exploratory, and we did not conduct post hoc power calculations for these endpoints.³⁵

Randomisation and blinding

A computer-generated randomisation sequence was used with gender-stratified permuted blocks of random sizes 4 and 6. A project member not involved in outcome assessments informed patients of group allocation, whereas all study personnel involved in outcome assessments were blinded to group allocation.

Patient and public involvement

Two patient representatives have participated in the ExeHeart project group from study inception. They have contributed with choice of outcome measures, trial implementation and interpretation of results.

Statistical analysis

Data are presented as means with SD, median with IQR and frequency with percentages. Intention-to-treat analysis was used, including all available data at the relevant time points. Missing data were assumed to be missing at random, and for the primary outcome, multiple imputation was used with 20 imputed sets for each missing entry. Analysis of covariance (ANCOVA) was applied to 3-month and 6-month follow-up data to assess mean group differences with age, gender and respective baseline value as covariates. ANCOVA model assumptions were assessed by homogeneity of variance (Levene's test), linearity of relationships and normality of residuals. Bootstrap CIs with 10 000 replications were applied if residuals were skewed. Wilcoxon rank sum was used for outcome variables with less than 30 observations in the total sample (SCORE2 and measures of self-reported burden of disease). Change in disease activity category was generated using paired data (baseline to 3 months and baseline to 6 months) and all categorical data were analysed by χ^2 tests.

Prespecified per-protocol analysis for the primary outcome at 3-month follow-up was conducted including only patients in the exercise group that adhered to the HIIT intervention and patients in the control group that reported <1 endurance exercise session/week.²⁴

A p value of 0.05 was considered significant and CIs are presented at the 95% level with no adjustments for multiple testing. STATA V.16.1 was used for all statistical analyses.

RESULTS

Participant flow and characteristics

From August 2021 to August 2022, 113 patients were screened for eligibility, and ultimately 60 patients were

enrolled in the ExeHeart trial. As shown in [figure 1](#), a total of 55 patients (92%) completed all outcome measures at 3-month and 6-month follow-up. Among the enrolled participants, 27 (45%) had RA, 19 (32%) had SpA and 14 (23%) had PsA, while 49 (82%) patients were classified as having an increased CVD risk. Baseline characteristics are provided in [table 2](#) and online supplemental table a.

Adherence and safety

In the exercise group, 27 training diaries were returned. On average, participants attended 18 (SD 5) out of 24 HIIT sessions, and 19 patients (70%) adhered to $\geq 70\%$ of the scheduled sessions (≥ 17 out of 24 sessions). In the completed HIIT sessions, mean exercise intensity at the third minute of each interval bout was 92% (SD 1) of HR_{peak} and mean Borg RPE 6–20 was 16 (SD 1). Mean attendance to non-supervised exercise sessions at moderate intensity was 11 (SD 4) out of 12 sessions. During these sessions, mean intensity was recorded as 72% (SD 1) of HR_{peak} , with a mean Borg RPE 6–20 of 14 (SD 2).

Throughout the study period, there were 18 cases of SARS-CoV-2 infection among patients from baseline to 3 months and an additional 14 cases from 3 months to 6 months, with no between-group difference in incidence (online supplemental table d). Two moderate adverse events were reported in the exercise group: One patient suffered from knee pain following exercise performed adjuvant to the HIIT protocol. One patient with a prior history of heart palpitations experienced irregular heart rate during two consecutive HIIT sessions. Said patient was offered an exercise ECG with unblinded study personnel. The test was deemed normal and the patient recommenced the HIIT intervention with no further complications. Within the control group, one serious and one moderate adverse event occurred, both unrelated to study visits: One patient in the control group experienced atrial flutter prior to study close-out and was hospitalised for further examinations, while the other patient suffered from a head concussion and waived further exercise tests.

At 3-month follow-up, disease flares were observed in one patient in the exercise group and two patients in the control group.

Efficacy on primary outcome

Following 12 weeks of HIIT, the exercise group showed a 2.5 mL/kg/min (95% CI 0.9 to 4.0) difference in change in VO_{2peak} at 3-month follow-up compared with the control group. The group difference in VO_{2peak} in favour of the exercise group was maintained at 6-month follow-up, with a mean difference of 2.6 mL/kg/min (95% CI 0.8 to 4.3) ([tables 3 and 4](#) and [figure 2](#)). Sensitivity analyses of complete case data showed similar results for the primary outcome (online supplemental tables b and c). Per-protocol analysis revealed a significant difference of 3.2 mL/kg/min (95% CI 1.7 to 4.8) in VO_{2peak} at 3-month follow-up between the 19 (70%) exercise group patients who completed at $\geq 17/24$ HIIT sessions versus the 20

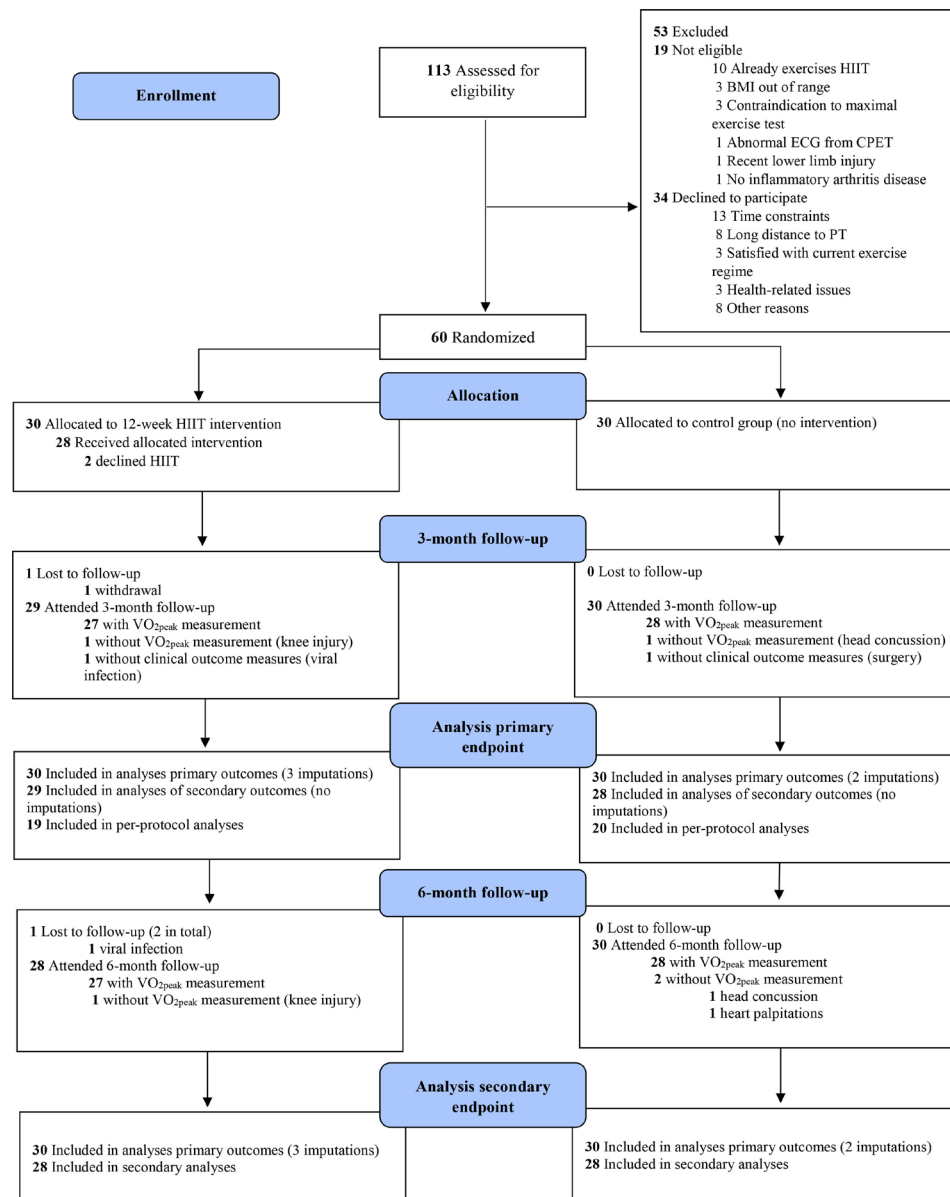


Figure 1 Consolidated Standards of Reporting Trials flow diagram of study enrolment, allocation and follow-up in the ExeHeart trial. BMI, body mass index; CPET, cardiopulmonary exercise test; HIIT, high-intensity interval training; PT, physiotherapist; VO_{2peak} , peak oxygen uptake.

(71%) control group participants who did not engage in regular aerobic exercise (online supplemental table b). No significant between-group changes were observed in end criteria for VO_{2peak} at 3-month and 6-month follow-up (table 5). While a significant difference in peak ventilation (5.8 L/min, 95% CI 0.5 to 11.0) was observed in favour of the exercise group at 3 months, there was no corresponding difference between groups at 6 months.

Efficacy on secondary outcomes

Tables 3 and 4 present secondary outcomes at 3-month and 6-month follow-up, respectively. After HIIT, there were significant group differences in VO_{2peak} measured as absolute capacity, VO_{2peak} relative to FFM and oxygen pulse in favour of the exercise group at 3-month and 6-month follow-up. There were no significant group differences

in anthropometry, resting heart rate, blood pressure and blood biochemistry at follow-up timepoints. The exercise group showed a higher proportion of patients being reclassified to lower disease activity category during follow-up compared with the control group. However, there were no significant group differences in change of disease activity category at 3-month ($\chi^2=8.3$, $p=0.08$) and 6-month follow-up ($\chi^2=9.8$, $p=0.08$). No significant differences were observed between the groups in terms of patient-reported pain, fatigue or exercise beliefs and self-efficacy at follow-up timepoints. Favourable changes in self-reported physical activity were observed in the exercise group compared with the control group at 3 months (7.0 points, 95% CI 3.3 to 10.7) and 6 months (4.7 points, 95% CI 0.1 to 9.4). At 6-month follow-up, a

Table 2 Baseline characteristics for all patients, the exercise group, and the control group

	All, n=60	Exercise group, n=30	Control group, n=30
Gender, female, n (%)	34 (57)	17 (57)	17 (57)
Age, years, median (IQR)	59 (52–63)	60 (51–63)	59 (53–63)
BMI, kg/m ² , median (IQR)	25 (22–30)	24 (22–27)	26 (23–26)
Relationship status, cohabits, n (%)	41 (70)	24 (80)	17 (57)
Education, >12 years, n (%)	46 (77)	24 (80)	22 (73)
Full-time employment, n (%)	34 (57)	17 (57)	17 (57)
Current smoker/snuff user, n (%)	13 (22)	3 (10)	10 (33)
IA duration, years, median (IQR)	16 (7–30)	13 (6–31)	18 (10–30)
Cardiorespiratory fitness			
VO _{2peak} mL/kg/min, mean (SD)	30.2 (6.9)	30.4 (5.9)	30.1 (7.9)
VO _{2peak} L/min, mean (SD)	2.35 (0.68)	2.32 (0.75)	2.40 (0.62)
Comorbidity			
Atherosclerosis/carotid plaque, n (%)	33 (55)	16 (53)	17 (57)
Diabetes, n (%)	3 (5)	0 (0)	3 (10)
Chronic obstructive pulmonary disease, n (%)	5 (8)	3 (10)	2 (7)
Inflammatory bowel disease, n (%)	5 (8)	4 (13)	1 (3)
IA medication			
Conventional DMARDs, n (%)	25 (42)	12 (40)	13 (43)
Biologics and/or JAK inhibitors, n (%)	43 (72)	21 (70)	22 (73)
Corticosteroids, n (%)	13 (22)	7 (23)	6 (21)
NSAIDs, n (%)	36 (60)	19 (63)	17 (57)
CVD medication			
Statins, n (%)	34 (57)	17 (57)	17 (57)
Beta-blockers, n (%)	2 (3)	1 (3)	1 (3)
Antihypertensives, n (%)	12 (20)	5 (17)	7 (23)
Analgesics			
Non-opioids, n (%)	42 (70)	22 (73)	20 (67)
Opioids, n (%)	7 (12)	4 (14)	3 (10)
Strong opioids, n (%)	0 (0)		

BMI, body mass index; CVD, cardiovascular disease; DMARDs, disease-modifying antirheumatic drugs; IA, inflammatory arthritis; JAK, Janus kinase; NSAIDs, non-steroidal anti-inflammatory drugs; VO_{2peak}, peak oxygen uptake.

significant difference was found in self-reported exercise habits between the two groups. Specifically, 18 (64%) patients in the exercise group reported engaging in aerobic exercise ≥ 1 per week in the past 3 months, while 8 (27%) patients in the control group reported the same ($\chi^2=8.3$, $p<0.01$, online supplemental table e).

DISCUSSION

In this assessor-blinded RCT, a 12-week HIIT programme delivered in physiotherapy primary care improved CRF in patients with IA, with beneficial effects on oxygen uptake sustained at the 6-month follow-up. The impact on secondary outcomes appeared modest and did not reach statistical significance, and the exercise intervention

demonstrated good tolerability with minimal adverse events and no increase in disease activity.

Increasing CRF through consistent exercise has favourable clinical implications as it enhances cardiovascular function,⁶ and our study adds to the growing body of evidence demonstrating positive effects of HIIT on CRF in various clinical populations.^{13–36} Notably, there is a scarcity of RCTs that have explored the effects of HIIT on improving CRF among patients with IA. The few existing studies focused on disease activity as the main outcome measure,^{21–22} although one of these studies also reported on CRF as the primary outcome.³⁷ Unlike the other RCTs on HIIT in IA conducted in specialised healthcare settings, our study delivered HIIT through physiotherapy

Table 3 Efficacy results from baseline to 3-month follow-up

	Exercise group			Control group			Estimated mean group difference (95% CI)*	P values	
	N	Baseline	3 months	N	Baseline	3 months			N
Primary outcome									
VO _{2peak} mL/kg/min	27	30.4 (5.9)	32.9 (6.4)	28	30.1 (7.9)	30.3 (7.5)	60†	2.5 (0.9 to 4.0)	<0.01‡
Secondary outcomes									
CPET									
VO _{2peak} L/min	27	2.3 (0.8)	2.5 (0.7)	28	2.4 (0.6)	2.4 (0.6)	60†	0.1 (0.1 to 0.2)	0.01‡
VO _{2peak} over fat-free mass (FFM), mL/FFM/min	27	42.7 (6.3)	45.9 (6.4)	27	43.6 (7.8)	44.0 (7.0)	54	2.7 (0.7 to 4.7)	0.01‡
Oxygen pulse, mL/beat/min§	26	14.4 (4.8)	15.7 (4.6)	28	14.2 (3.5)	14.6 (3.6)	55	0.9 (0.3 to 1.5)	0.01‡
Body composition									
BMI, kg/m ² , median (IQR)	28	24 (22–28)	24 (21–28)	29	26 (23–31)	27 (23–31)	57		0.24¶
FFM, kg	28	54.3 (12.6)	54.3 (13.2)	28	54.9 (11.4)	55.0 (11.5)	56	0.0 (-0.5 to 0.6)	0.9
Inflammatory markers									
CRP, mg/L	28	2.2 (3.0)	3.3 (5.9)	30	2.7 (2.7)	2.4 (2.4)	58	1.0 (-1.5 to 3.5)**	0.42
ESR, mm/hour	27	9.8 (7.3)	8.6 (5.9)	30	11.7 (8.8)	11.1 (7.4)	57	-1.3 (-3.9 to 1.2)**	0.31
Disease activity category	28			29			57		0.08††
Remission, n (%)		11 (39)	11 (39)		10 (34)	11 (38)			
Low, n (%)		6 (21)	10 (36)		10 (34)	5 (17)			
Moderate, n (%)		8 (29)	7 (25)		5 (17)	11 (38)			
High, n (%)		3 (11)	0 (0)		4 (14)	2 (7)			
Blood pressure and resting heart rate									
Systolic, mm Hg	28	125 (12)	127 (14)	29	129 (14)	126 (11)	57	3 (-2 to 8)	0.20
Diastolic, mm Hg	28	81 (10)	84 (12)	29	85 (8)	85 (9)	57	1 (-4 to 5)	0.72
Resting heart rate, beats/min§	27	64 (9)	61 (7)	29	73 (11)	69 (11)	56	-4 (-8 to 0)	0.08
Lipids									
Total cholesterol, mmol/L	28	5.0 (1.4)	4.4 (1.2)	30	4.6 (1.1)	4.2 (1.1)	58	0.1 (-0.5 to 0.6)	0.76
HDL-c, mmol/L	28	1.7 (0.5)	1.7 (0.6)	30	1.6 (0.5)	1.6 (0.5)	58	0.1 (-0.0 to 0.2)	0.15
LDL-c, mmol/L	28	2.8 (1.3)	2.2 (1.1)	30	2.5 (1.1)	2.1 (1.1)	58	-0.0 (-0.5 to 0.5)	0.95
Triglycerides, mmol/L	28	1.3 (0.6)	1.4 (1.2)	30	1.4 (0.8)	1.3 (0.7)	58	0.2 (-0.2 to 0.6)**	0.28
NRS pain and fatigue									
Fatigue last week, 0–10, 0=no fatigue	29	3.1 (2.1)	3.0 (1.9)	30	3.6 (2.5)	3.5 (2.7)	59	-0.1 (-0.9 to 0.8)	0.87
Pain last week, 0–10, 0=no pain	29	2.9 (2.1)	2.8 (1.8)	30	2.9 (2.5)	3.1 (2.7)	59	-0.3 (-1.3 to 0.7)**	0.57

Continued

Table 3 Continued

	Exercise group			Control group			Estimated mean group difference (95% CI)*	P values
	N	Baseline	3 months	N	Baseline	3 months		
Physical activity index, 0–45 points, 45=best	29	7.8 (8.6)	16.6 (8.8)	30	4.2 (8.0)	7.8 (7.8)	7.0 (3.4 to 10.7)**	<0.01‡
Exercise beliefs and self-efficacy, 0–100 points, 100=best	26	81.9 (7.5)	81.4 (8.1)	26	77.3 (9.1)	77.3 (8.8)	0.6 (–2.7 to 3.9)	0.72

Values are presented as mean (SD) unless otherwise indicated.
 *Analysed with ANCOVA with gender, group, age at baseline and baseline value as covariates.
 †Primary analysis with multiple imputation of estimate.
 ‡Significant differences.
 §Patients with change in beta-blocker medication from baseline (n=1) omitted from analysis.
 ¶Analysed with Wilcoxon rank sum.
 **Bootstrap CI with 10 000 replications.
 ††Analysed with χ^2 test.
 ANCOVA, analysis of covariance; BMI, body mass index; CPET, cardiopulmonary exercise test; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NRS, Numerical Rating Scale; VO_{2peak}, peak oxygen uptake.

primary care and illustrates the feasibility of HIIT as an effective exercise intervention that can be used in the management of IA in primary care settings. We found that the exercise group attained a 2.5 mL/kg/min higher VO_{2peak} following the intervention, consistent with the 2.7 mL/kg/min improvement in estimated CRF reported in the ES_{PA} trial.²¹ Compared with our results, Thomsen *et al*³⁷ reported a higher increase in VO_{2peak} following HIIT in patients with PsA. This difference could be attributed to the frequency of HIIT sessions, as the study by Thompson *et al* conducted three weekly HIIT sessions, whereas our study involved two weekly HIIT sessions and one session at moderate intensity. Moreover, two pilot studies using pre–post³⁸ and cross-over³⁹ designs support the beneficial effects of HIIT on CRF in the context of IA. While our estimate of effect falls short of the 3.5 mL/kg/min increase in CRF that is commonly associated with substantial risk reduction in epidemiological studies,⁸ it is important to recognise that even smaller improvements, such as 1 mL/kg/min, have been linked to notable health benefits and lower risk of CVD and all-cause mortality.^{7, 40} Furthermore, our results demonstrate a significant increase in VO_{2peak} measured in terms of absolute capacity and adjusted to FFM, indicating an improvement in CRF independent of changes in weight and body composition. Additionally, we observed a concurrent rise in oxygen pulse, serving as a surrogate marker for stroke volume, subsequent to HIIT. This aligns with the notion that the changes observed in VO_{2peak} following HIIT are largely driven by enhancements in stroke volume.⁴¹ Given the elevated CVD risk faced by patients with IA, time-efficient HIIT interventions that promote CRF can play a vital role in mitigating this risk.

Despite concerns about the long-term effects of HIIT, particularly the potential decline in CRF once the supervised exercise intervention is ceased,¹⁴ our study provides evidence to the contrary. We found that the beneficial increase in CRF remained consistently strong at 6-month follow-up. Furthermore, patients in the exercise group presented with higher physical activity indexes at follow-up as well as greater engagement in aerobic exercise between the 3-month and 6-month follow-up compared with those in the control group. This suggests a sustained adherence to an active lifestyle among the exercise group. Our findings align with a study conducted by Thomsen *et al*,³⁷ which observed sustained effects of HIIT in patients with PsA at 9-month follow-up. These results underscore the potential of HIIT as a long-term strategy for enhancing CRF in individuals with IA.

While our ITT analyses provide estimates that may reflect real-world conditions, the per-protocol analysis focuses on patients that adhered to the exercise plan and offers insights into the optimal treatment effects of HIIT on CRF.⁴² In our study, the per-protocol analysis revealed a notable increase of 3.2 mL/kg/min in CRF among patients who adhered to $\geq 70\%$ of the HIIT sessions. This improvement closely approaches the 3.6 mL/kg/min reported in a smaller study by Haglo *et al*,⁴³



Table 4 Efficacy results from baseline to 6-month follow-up

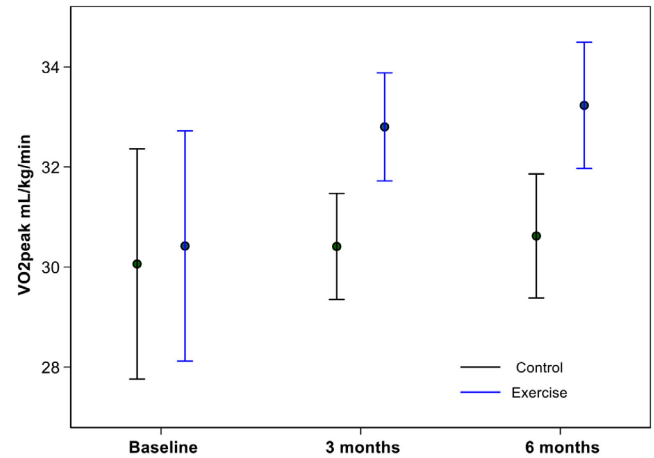
	Exercise group		Control group		Estimated mean group difference (95% CI)*	P values			
	N	Baseline	6 months	N			Baseline	6 months	N
Primary outcome									
VO _{2peak} , mL/kg/min	27	30.4 (5.9)	33.2 (7.4)	28	30.4 (8.0)	30.7 (7.8)	60†	2.6 (0.8 to 4.3)	<0.01‡
Secondary outcomes									
CPET									
VO _{2peak} , L/min	27	2.3 (0.8)	2.5 (0.7)	28	2.4 (0.6)	2.4 (0.6)	60†	0.1 (0.1 to 0.3)	0.02‡
VO _{2peak} over fat-free mass (FFM), mL/FFM/min	27	42.7 (6.3)	46.4 (7.6)	27	43.8 (7.8)	44.3 (7.9)	54	3.1 (0.8 to 5.4)	0.01‡
Oxygen pulse, mL/beat/min§	27	14.4 (4.7)	15.7 (5.0)	28	14.2 (3.5)	14.6 (3.6)	55	1.0 (0.4 to 1.7)¶	<0.01‡
Body composition									
BMI, kg/m ² , median (IQR)	28	24 (22–28)	24 (21–27)	30	26 (23–31)	26 (23–30)	57		0.55**
FFM, kg	28	54.3 (12.6)	54.0 (12.8)	29	55.2 (11.2)	55.4 (11.5)	57	-0.5 (-1.4 to 0.4)	0.24
Inflammatory markers									
CRP, mg/L	28	2.2 (3.0)	2.4 (4.0)	30	2.7 (2.7)	2.2 (1.6)	58	0.5 (-0.9 to 2.0)¶	0.47
ESR, mm/hour	26	9.3 (7.0)	8.8 (7.1)	28	11.7 (9.1)	10.4 (6.7)	54	-0.0 (-2.8 to 2.7)¶	0.98
Disease activity category	28			30			58		0.08††
Remission, n (%)		11 (39)	14 (50)		10 (34)	10 (33)			
Low, n (%)		6 (21)	7 (25)		11 (37)	7 (23)			
Moderate, n (%)		8 (29)	6 (21)		5 (17)	10 (33)			
High, n (%)		3 (11)	1 (4)		4 (13)	3 (107)			
Blood pressure and resting heart rate									
Systolic, mm Hg	28	125 (12)	127 (13)	30	128 (14)	126 (13)	58	4 (-1 to 9)¶	0.14
Diastolic, mm Hg	28	81 (10)	84 (10)	30	85 (8)	83 (9)	58	3 (-1 to 6)¶	0.18
Resting heart rate, beats/min§	27	64 (9)	63 (8)	29	72 (12)	67 (8)	56	-0 (-4 to 3)	0.9
Lipids									
Total cholesterol, mmol/L	28	5.0 (1.4)	4.3 (1.1)	30	4.6 (1.1)	4.1 (1.1)	58	0.2 (-0.4 to 0.7)	0.55
HDL-c, mmol/L	28	1.7 (0.5)	1.8 (0.6)	30	1.6 (0.5)	1.6 (0.6)	58	0.2 (-0.1 to 0.4)	0.13
LDL-c, mmol/L	28	2.8 (1.3)	2.1 (0.9)	30	2.5 (1.1)	2.0 (1.0)	58	0.1 (-0.4 to 0.5)	0.7
Triglycerides, mmol/L	28	1.3 (0.6)	1.3 (1.0)	30	1.4 (0.8)	1.4 (0.8)	58	-0.1 (-0.4 to 0.3)¶	0.69
NRS pain and fatigue									
Fatigue last week, 0–10, 0=no pain	28	3.1 (2.1)	3.1 (2.2)	30	3.6 (2.5)	3.8 (2.4)	58	-0.4 (-1.2 to 0.5)¶	0.41
Pain last week, 0–10, 0=no pain	28	2.9 (2.2)	2.9 (2.0)	30	2.9 (2.5)	3.2 (2.4)	58	-0.4 (-1.2 to 0.5)	0.38

Continued

Table 4 Continued

	Exercise group			Control group			Estimated mean group difference (95% CI)*	P values
	N	Baseline	6 months	N	Baseline	6 months		
Physical activity index, 0–45 points, 45=best	28	7.6 (8.9)	14.4 (12.1)	30	4.2 (8.0)	7.8 (7.8)	4.7 (0.1 to 9.4)¶	0.05‡
Exercise beliefs and self-efficacy, 0–100 points, 100=best	26	81.5 (7.0)	82.4 (8.7)	27	79.7 (9.9)	78.2 (11.3)	2.7 (–1.6 to 6.4)¶	0.15

Values are presented as mean (SD) unless otherwise indicated.
 *Analysed with ANCOVA with gender, group, age at baseline and baseline value as covariates.
 †Primary analysis with multiple imputation of estimate.
 ‡Significant differences.
 §Patients with change in beta-blocker medication from baseline (n=2) omitted from analysis.
 ¶Bootstrap CI with 10 000 replications.
 **Analysed with Wilcoxon rank sum.
 ††Analysed with χ^2 test.
 ANCOVA, analysis of covariance; BMI, body mass index; CPET, cardiopulmonary exercise test; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FFM, fat-free mass; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NRS, Numerical Rating Scale; VO_{2peak}, peak oxygen uptake.



Adjusted means with 95% CI (ITT population)

Figure 2 Mean VO_{2peak} in mL/kg/min across groups and study visits. Error bars represent 95% CI of means adjusted by covariates from analysis of covariance; age, gender and baseline value. Control group is shown in grey and exercise group in blue. Between-group difference at 3 months was 2.5 mL/kg/min (95% CI 0.9 to 4.0, $p < 0.01$) and at 6 months 2.6 mL/kg/min (95% CI 0.8 to 4.3, $p < 0.01$). ITT, Intention to Treat; VO_{2peak}, peak oxygen uptake in mL/kg/min.

which investigated the per-protocol effect of supervised versus app-based HIIT in patients with IA. These findings emphasise the importance of adhering to an exercise programme to maximise the benefits on CRF.

Although HIIT has been established as beneficial for cardiometabolic health in the general population,¹³ there is a paucity of research examining the impact of HIIT on classic CVD risk factors in individuals with IA. In the present study, we observed no significant results in the secondary outcomes related to CVD risk factors, which aligns with the findings of two pilot studies conducted in patients with RA.^{39,44} However, other studies have reported favourable changes in body composition and waist circumference in patients with PsA³⁷ and SpA²¹ following HIIT, and in patients with RA, a 6-month moderate intensity exercise programme improved blood pressure, lipid levels⁴⁵ and endothelial function.⁴⁶ It is important to highlight that although over 80% of the individuals in our study presented with an increased CVD risk, a considerable number of patients had prescribed antihypertensives and/or statins, and baseline levels of blood pressure and lipids were within recommended target levels. This efficient management of traditional CVD risk factors at the onset of the study may have limited the potential for further adaptation in response to exercise.

There is some evidence indicating that appropriately prescribed exercise can improve disease activity in patients with IA,⁴⁷ similar to the positive changes in inflammatory markers observed in healthy middle-aged and older individuals.¹⁶ HIIT has been found to improve disease activity in patients with SpA,²¹ while studies in patients with PsA²² and RA³⁹ have reported no significant impact on disease activity. In the present study, we observed

Table 5 Ventilation and common VO_{2peak} end criteria from cardiopulmonary exercise tests at baseline, 3 months and 6 months

	Exercise group (n=27)	Control group (n=28)	Estimated mean group difference (95% CI)*	P values
Baseline				
V_E at peak exercise, L/min	88.1 (28.3)	89.0 (25.4)	NA	NA
Peak heart rate, beats/min	163 (16)	168 (12)		
Respiratory exchange ratio, VCO_2/VO_2	1.16 (0.08)	1.16 (0.06)		
Borg RPE 0–10, 10=max, median (IQR)	10 (9–10)	10 (9–10)		
Lactate, median (IQR)	9.0 (7.3–11.4)†	9.4 (7.8–12.0)		
3 months				
V_E at peak exercise, L/min	93.8 (27.5)	88.8 (25.4)	5.8 (0.5 to 11.0)	0.03‡
Peak heart rate, beats/min	162 (15)	165 (12)	0.4 (–2.7 to 3.5)	0.81
Respiratory exchange ratio, VCO_2/VO_2	1.15 (0.07)	1.15 (0.06)	0.01 (–0.02 to 0.04)	0.61
Borg RPE 0–10, 10=max, median (IQR)	10 (9–10)	10 (9–10)		0.32§
Lactate, mmol/L, median (IQR)	8.0 (6.3–12.7)†	10.1 (8.2–12.2)		0.73§
6 months				
V_E at peak exercise, L/min	93.9 (28.2)	91.1 (24.7)	3.4 (–1.9 to 8.7)	0.21
Peak heart rate, beats/min	161 (16)	164 (10)	–1 (–4 to 3)	0.7
Respiratory exchange ratio, VCO_2/VO_2	1.14 (0.09)	1.16 (0.06)	–0.02 (–0.06 to 0.01)	0.16
Borg RPE 0–10, 10=max, median (IQR)	10 (9–10)	10 (9–10)		0.64§
Lactate, mmol/L, median (IQR)	9.5 (6.8–13.6)†	9.6 (7.5–12.2)¶		0.89§
Values are presented as mean (SD) unless otherwise indicated.				
*Analysed with ANCOVA with gender, group, age at baseline and baseline value as covariates.				
†n=24.				
‡Significant differences.				
§Analysed with Wilcoxon rank sum.				
¶n=22				
ANCOVA, analysis of covariance; Borg RPE, Borg rating of perceived exertion; VCO_2 , volume of carbon dioxide production; V_E , minute ventilation; VO_2 , volume of oxygen uptake; VO_{2peak} , peak oxygen uptake.				

no significant effects of HIIT on serum inflammatory markers. However, baseline levels of inflammatory values were low, and this may have introduced a floor effect and limited the potential for substantial change. Despite the lack of significant group differences, a higher number of patients in the exercise group were reclassified to a lower disease activity category at follow-up timepoints. Although disease activity category is a coarse classification, it combines the patient's subjective perception of disease activity along with objective clinical measures.⁴⁸ Therefore, an improvement in disease activity category could be interpreted as an overall improvement in disease impact.

Future research is needed to investigate the effects of HIIT on inflammatory markers and CVD risk factors, especially in patients not receiving CVD preventive medication. Considering the high prevalence of carotid plaque in our study sample and the potential of HIIT to reduce atheroma volume,⁴⁹ studying the impact of HIIT on coronary plaque in individuals with IA may also be an interesting avenue for further research.

Strengths and limitations

Strengths of the current study include its randomised controlled design, assessor-blinded approach, intention-to-treat analyses and use of the CPET criterion method to measure CRF.

Several limitations should be acknowledged. First, our study sample likely consisted of motivated individuals and a possible selection bias may limit the generalisability of our findings to the broader IA population. Second, our a priori power calculation was based on the primary outcome, potentially leading to insufficient power to detect differences in secondary outcomes. We recognise that despite employing an RCT design, chance imbalance between groups may arise, as indicated by the higher proportion of smokers and longer disease duration in the control group. However, considering the comparable spirometry values and self-reported measures of disease burden in both groups (online supplemental table a), we do not believe this had a substantial impact on study results. Despite no group differences in SARS-CoV-2 incidence, we cannot rule out the possibility that a SARS-CoV-2 infection could have blunted the response

to HIIT in the exercise group. Moreover, lack of blinding among patients may have introduced bias in self-reported outcomes. Additionally, the therapeutic effect of several CPET sessions could have motivated the control group and influenced outcomes by triggering them to engage in vigorous exercise. Lastly, the use of bioelectrical impedance analysis has limitations in accuracy,⁵⁰ which could affect the validity of measures of body composition.

CONCLUSION

This study demonstrates improvements in CRF, measured as peak oxygen uptake, in patients with IA following 12 weeks of supervised exercise at high intensity delivered in physiotherapy primary care, compared with usual care. The positive effects on oxygen uptake were maintained at 6-month follow-up. The HIIT intervention was well tolerated, with minimal adverse events and no negative impact on disease activity. These findings support the integration of HIIT as an effective and feasible physiotherapy intervention in primary care for patients with IA.

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Wyeth, Sanofi, Novartis, Pfizer and Lilly and is secretary of ESC Cardiovascular Pharmacotherapy working group.

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

Ethics approval This study involves human participants and was approved by the Regional Committee for Medical and Health Research Ethics (201227) and the data protection officer at Diakonhjemmet Hospital (reg. no. 00397). Participants gave informed consent to participate in the study before taking part and study procedures aligned with the Declaration of Helsinki.

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