BMJ Open

# Effect of high-intensity exercise on cardiorespiratory fitness, cardiovascular disease risk and disease activity in patients with inflammatory joint disease: protocol for the ExeHeart randomised controlled trial

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**To cite:** Nordén KR, Dagfinrud H, Semb AG, *et al*. Effect of high-intensity exercise on cardiorespiratory fitness, cardiovascular disease risk and disease activity in patients with inflammatory joint disease: protocol for the ExeHeart randomised controlled trial. *BMJ Open* 2022;**12**:e058634. doi:10.1136/bmjopen-2021-058634

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058634).

Received 22 October 2021
Accepted 28 January 2022



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## ABSTRACT

**Introduction** Inflammatory joint disease (IJD) is associated with increased risk of cardiovascular disease (CVD) fostered by systemic inflammation and a high prevalence of CVD risk factors. Cardiorespiratory fitness (CRF) is an important health parameter and CRF-measures are advocated in routine health evaluations. CRF associates with CVD risk, and exercise modalities such as high intensity interval training (HIIT) can increase CRF and mitigate CVD risk factors. In IJD, exercise is rarely used in CVD risk management and the cardioprotective effect of HIIT is unclear. Furthermore, the clinical applicability of HIIT to primary care settings is largely unknown and warrants investigation. The primary aim is to assess the effect of a HIIT programme on CRF in patients with IJD. Second, we will evaluate the effect of HIIT on CVD risk and disease activity in patients with IJD, feasibility of HIIT in primary care and validity of non-exercise algorithms to detect change in CRF.

**Methods and analysis** ExeHeart is a single-blinded, randomised controlled trial. Sixty patients with IJD will be recruited from the Preventive Cardio-Rheuma clinic at Diakonhjemmet Hospital, Norway. Patients will be assigned to receive standard care (relevant lifestyle advice and cardio-preventive medication) or standard care plus a 12-week HIIT intervention by physiotherapists in primary care. HIIT sessions will be prescribed at 90%–95% of peak heart rate. Outcomes include CRF (primary outcome), CVD risk factors, anthropometric measures, disease activity and patient-reported outcomes related to pain, fatigue, disease, physical activity and exercise and will be assessed at baseline, 3 months (primary endpoint) and 6 months postbaseline.

**Ethics and dissemination** Ethical approval has been obtained from the Regional Committee for Medical and Health Research Ethics (201227). Participants are required to sign a written informed consent form. Results will be discussed with patient representatives, submitted to peer-reviewed journals and presented at relevant platforms.

**Trial registration number** NCT04922840.

## Strengths and limitations of this study

- The ExeHeart trial is developed in collaboration with patient research partners and aligns with patient's requests of viable, non-pharmacological treatment alternatives in inflammatory joint disease.
- The high-intensity exercise intervention is set in physiotherapy primary care, thereby strengthening the generalisability of trial results to daily clinical care.
- Robust randomised controlled design with repeated assessment of outcome measures by renowned methods is a strength.
- Limited by the use of only one exercise modality and effect sizes are not transferable to endurance exercise at other intensities.
- Non-blinding of patients to study hypothesis and the use of a cardiopulmonary exercise test can prompt changes in physical activity behaviour and diminish group differences at follow-up assessments and is considered a limitation.

## INTRODUCTION

Inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), spondyloarthritis (SpA) and psoriatic arthritis (PsA), are inflammatory autoimmune diseases with common traits of joint inflammation, pain, stiffness, fatigue and reduced physical function.[1 2] Compared to the general population, individuals with IJD have an increased risk of cardiovascular disease (CVD).[3–5] Systemic inflammation can accelerate processes that lead to atherosclerosis and chronic inflammation, and this has been identified as an independent risk factor of CVD.[6 7] The elevated CVD risk is also attributed to a higher

prevalence and burden of traditional risk factors such as hypertension, obesity and hyperlipidaemia.[8–10] Furthermore, cardiorespiratory fitness (CRF) is recognised as a clinically important variable given that low levels of CRF are associated with higher risk of CVD and all-cause mortality.[11] Inferior levels of physical activity and CRF are reported in patients with IJD[12 13] and may serve as a further catalyst in the elevated CVD risk for this patient group.[14 15] Implementation of interventions that can mitigate both systemic inflammation and prevalent CVD risk factors is therefore essential to reduce the risk of CVD in patients with IJD.[8]

CVD prevention in patients with IJD is advocated and the European Alliance of Associations for Rheumatology (EULAR) advises routine CVD screening for patients with IJD.[3] Despite increased awareness of excess CVD risk, management is often suboptimal and CVD risk factors are frequently non-recorded and undertreated in patients with IJD.[16 17] Common CVD risk prediction models underestimate the risk of CVD in the context of IJD,[18] a fact that accentuates the need for additional health measures to optimise CVD risk evaluation in this high-risk population.[16] Routine assessment of CRF as a clinical vital sign is recommended, but seldom performed in outpatient settings. However, user-friendly, non-exercise algorithms to estimate CRF (eCRF) are available and can potentially be used to measure the effect of health-enhancing interventions in IJD care.[11 19]

Physical activity is currently included in guidelines on primary and secondary prevention of CVD and individuals presenting with CVD as primary diagnosis are often referred to exercise as an integral part of disease management.[7 20] However, exercise is underutilised as a core component of CVD risk management in patients with IJD and seldom implemented in clinical healthcare.[21 22] Previous hesitancy regarding the safety of vigorous exercise has led to rather conservative dosage of exercise intensity in IJD, but recent studies demonstrate that vigorous exercise is safe and does not inflict disease flares in patients with IJD.[23–25] Research even indicates that exercise may promote an anti-inflammatory milieu, although additional studies are required to conclude on the exercise-induced effect on inflammation in the presence of IJD.[26 27]

Exercise has a dose-dependent effect on health outcomes and high-intensity interval training (HIIT) has emerged as a form of exercise that is proven superior to exercise at lower intensities in improving CRF.[28 29] This time-efficient exercise mode alternates between bouts of high intensity exercise interspaced with bouts of lower intensity. Beneficial health outcomes of HIIT have been reported in various patient populations, but additional studies are needed to safely recommend HIIT as a cardioprotective mode of exercise in patients with IJD.[30 31] Notably, HIIT interventions are often delivered under stringent research designs or with care providers that are extensively trained in the patient group at hand. This has cast doubt on the applicability of HIIT in real world contexts and studies evaluating the effect of HIIT in routine clinical care are currently needed.[32]

### Aim

The primary aim of the ExeHeart trial is to determine the effect of a 12-week HIIT programme set in physiotherapy primary care on CRF in patients with IJD.

Secondary aims of the trial are to (1) assess the effect of HIIT on traditional CVD risk factors and disease activity in patients with IJD, (2) assess the association between CRF and disease-specific and CVD-related variables in IJD, (3) explore the feasibility of a HIIT intervention set in physiotherapy primary care in terms of patient's adherence and tolerability to the exercise programme and (4) report on the validity of eCRF algorithms to accurately detect potential changes in CRF.

### Hypotheses

We hypothesise that the HIIT intervention set in primary care will increase CRF and be associated with a concurrent decrease in traditional CVD risk factors. We do not expect any increase in disease activity due to HIIT. The HIIT intervention in primary care is hypothesised to be feasible measured by patient adherence and tolerability. Finally, we hypothesise that eCRF can detect meaningful change in CRF.

## METHODS AND ANALYSIS

### Trial design and study setting

ExeHeart is a parallel group, randomised controlled superiority trial with repeated measures. Patients will be randomly allocated to (1) Current clinical practice including CVD risk evaluation, lifestyle advice given at baseline and relevant cardioprotective medication (control group) or (2) Current clinical practice and a 12-week HIIT intervention. The HIIT intervention will be supervised by experienced and licensed physiotherapists at primary care clinics in the municipality of Oslo, Norway.

Patients will be recruited from the Preventive Cardio-Rheuma clinic, an outpatient clinic housed by the Department of Rheumatology and Research at Diakonhjemmet Hospital, Oslo, Norway. Referral criteria to the Preventive Cardio-Rheuma clinic are (1) Patient with IJD requesting a CVD risk evaluation, (2) Physician or patient are aware of the presence of ≥1 CVD risk factors, (3) Patient with symptoms consistent with CVD risk factors, for example, headache due to increased blood pressure and/or (4) Patient with a family history of premature CVD.[33]

### Project timeline

Enrolment was initiated in August 2021 and will continue until target sample size is reached, presumably by October 2022. Participant flow is illustrated in figure 1. The unpredictable course of the ongoing SARS-CoV-2 pandemic may impact national healthcare systems and influence the ExeHeart trial progress. At baseline, measurements will

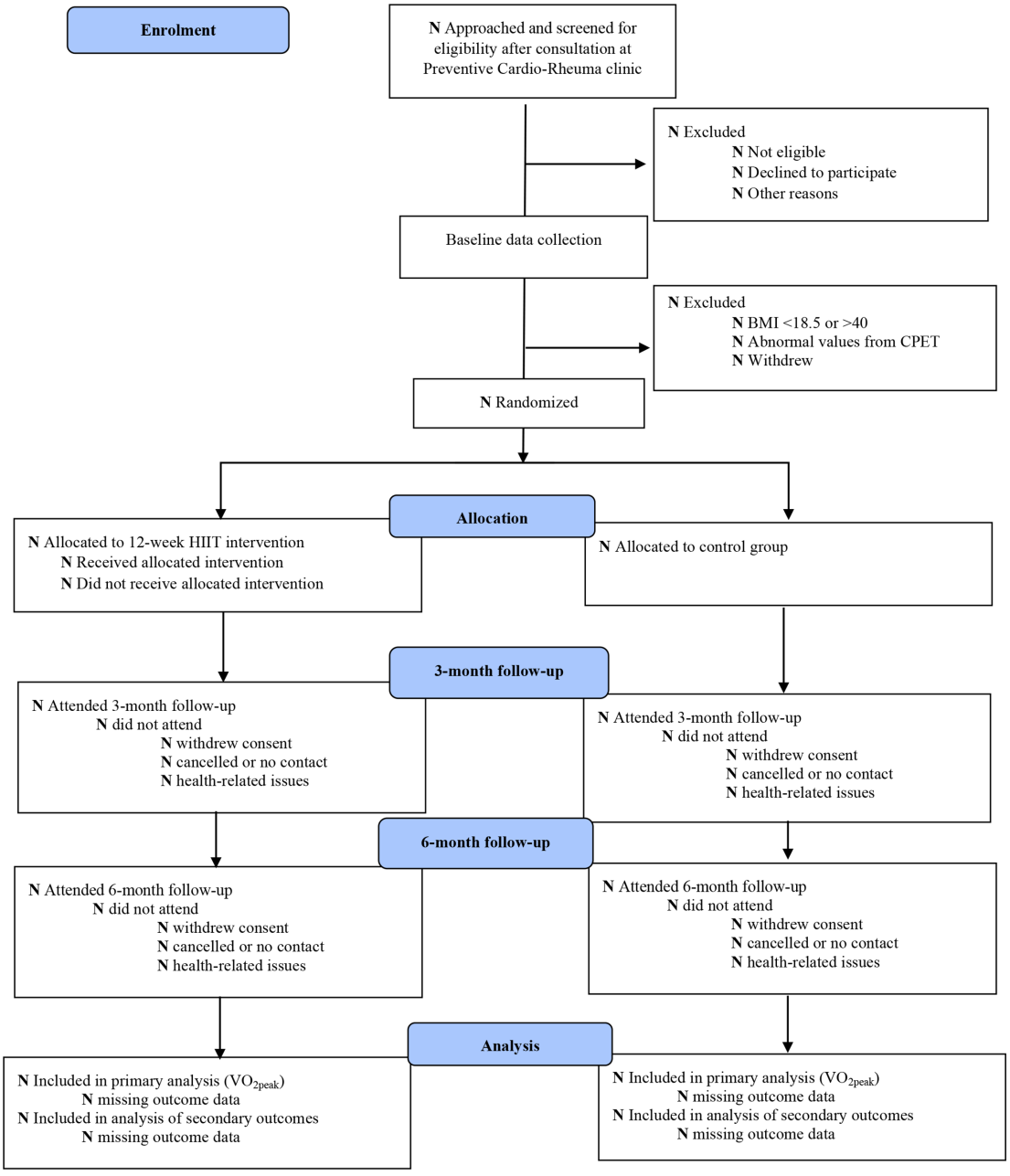


**Figure 1** Exeheart trial flow chart. BMI, body mass index; CPET, cardiopulmonary Exercise test; HIIT, high-intensity interval training; $VO_{2peak}$, peak oxygen uptake.

be collected from the patient's consultation at the Preventive Cardio-Rheuma clinic (prebaseline), digital questionnaires and a baseline clinical test session at the outpatient clinic at Diakonhjemmet Hospital. The full test protocol will be repeated at follow-up sessions that are scheduled 3 months and 6 months after baseline assessment.

## Sample size

Sample size is calculated on the basis of the primary outcome variable, where a between-group difference in peak oxygen uptake ($VO_{2peak}$) of 3.5 mL/kg/min is considered to be of clinical relevance.[20] Using a reported upper bound of 4.5 on the SD of change in $VO_{2peak}$ [34] and 80% power to detect this difference, approximately 25 participants are required in each group. To allow for a possible 20% drop-out rate, we plan to randomise 60 patients in total (ie, 30 per group).

## Eligibility criteria and patient screening

Patients will receive a cardiovascular risk evaluation by a cardiologist (AGS) at the Preventive Cardio-Rheuma clinic and be assessed for trial eligibility based on age, diagnosis and cardiovascular suitability to maximal exercise testing. Subsequently, patients will be contacted by an ExeHeart project group member and provided oral and written information regarding the purpose and requirements of the study. Patients will be screened thoroughly according to inclusion and exclusion criteria, including American College of Sports Medicine guidelines for exercise testing[20] (table 1). Eligible patients will be invited to

Table 1 ExeHeart inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| ► Age 18–70 years old at baseline<br>► BMI: 18.5–40 kg/m$^2$<br>► IJD disease verified by rheumatologist<br>► Able to walk unaided and continuously for ≥15 min<br>► Norwegian or English speaking | ► Sustained lower extremity injury ≤12 months, including surgery<br>► Primary neurological disease<br>► Contraindication to maximal exercise test[20]<br>► Cognitive disability<br>► Participation in structured HIIT ≥1 /week the last 3 months |

BMI, body mass index; HIIT, High-Intensity Interval Training; IJD, inflammatory joint disease.

enrol in the study and sign an informed consent form on acceptance of participation (online supplemental files A and B).

## Outcome measures

The primary outcome measure is CRF at 3-month follow-up, measured as $VO_{2peak}$ in mL/kg/min by a cardiopulmonary exercise test (CPET).

Secondary outcome measures comprise disease activity, blood pressure, blood lipids, body mass index, body composition, arterial stiffness, resting heart rate (HR), Systemic COronary Risk Estimation 2 (SCORE2), additional markers of CRF derived from CPET (table 2) and patient self-report of pain, fatigue, cardiovascular health, medication and domains related to physical activity and exercise (table 3).

### Cardiopulmonary exercise test

The CPET will be performed by use of a breath-by-breath gas analysing system (Vyntus CPX, Vyaire Medial, Hoechenberg, Germany) with gas calibration every third hour, automatic volume sensor calibration between each subject and weekly manual calibration of volume sensors by a 3 L syringe (Hans Rudolph, Shawnee, USA).[35]

To start with, pulmonary function will be assessed by spirometer according to guidelines[36] and forced expiratory volume (FEV1, L), forced vital capacity (L) and peak expiratory flow (L/min) will be recorded from three attempts at maximal expiratory flow volume loops. Maximal voluntary ventilation (MVV, L/min) will be measured twice by breathing deeply and rapidly for 12 s. In cases of poor technique, MVV will be estimated as FEV1×37.5 (35).

The CPET will be performed on a treadmill (PPS 55 Woodway, Würzburg, Germany) with 12-lead ECG (Customed cardio 300 BT_A, CareFusion, Ottobrunn, Germany), blood pressure monitor (Suntech Tango M2, SunTech Medical, Morrisville, USA), pulse oximetry and modified Borg rating of perceived exertion (Borg RPE 1–10).[37] Gas exchange is measured breath-by-breath and averaged over eight breaths throughout the test with patients breathing into a Hans Rudolph two-way mask (7450 series, Hans Rudolph, Shawnee, USA). A modified Balke ramp protocol is used with initial treadmill speed individually set based on estimated functional capacity.[38] Patients unaccustomed to treadmill walking will be familiarised with the treadmill before the test starts. The test is completed when the participant is unable to continue despite verbal encouragement from the test technician. The protocol is terminated in advance of exhaustion if the test technician observes abnormal and/or adverse test values or the patient requests to stop.[20] Peak HR ($HR_{peak}$) is recorded at maximal exercise level. Blood lactate concentration is sampled within 60 s of test completion to evaluate level of anaerobic processes (Lactate Scout 4, SensLab, Leipzig, Germany). Borg RPE 0–10, $HR_{peak}$, respiratory exchange ratio and post-exercise blood lactate concentration are used to assess level of effort.[39] Additional parameters collected from CPET are ventilatory thresholds, breathing reserve at peak exercise, oxygen pulse as well as ventilatory equivalents for oxygen and carbon dioxide.[11]

### Traditional CVD risk factors

Medical background information will be collected from the patient's journal recorded at the prebaseline consultation at the Preventive Cardio-Rheuma clinic. Non-fasting blood samples will be measured at the hospital laboratory (European Standard Accredited 2009) by routine procedures (Cobas 8000, F. Hoffmann-La Roche, Basel, Switzerland)[40] and analysed for C reactive protein (CRP), erythrocyte sedimentation rate (ESR), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein and triglycerides. Blood pressure, resting HR, and arterial stiffness (measured as augmentation index and pulse wave velocity) will be measured after the patient has been in a supine position for at least 10 min in a semi dark room, using an ambulatory blood pressure monitor (Mobil-o-graph PWA, I.E.M., Stolberg, Germany). Twelve-lead resting ECG will be recorded (CAM 14, GE Medical Systems Information Technologies, Wisconsin, USA). SCORE2 will be calculated with variables gender, age, non-HDL cholesterol, systolic blood pressure and smoking status.[7] As recommended by EULAR, a 1.5 multiplication factor will be included for patients presenting with RA.[3]

### Anthropometric measures

Patients will be asked to be 2 hours postprandial and to refrain from using caffeine and/or nicotine the last 4 hours prior to study visits. Body height will be measured by wall ruler (KaWe Person Check, Kirchner & Wilhelm+Co. KG, Asperg, Germany). Body weight and body composition will be measured by bioelectrical impedance analysis (Tanita MC-780MA and Tanita Gmon Software Pro, Tanita, Tokyo, Japan). Waist circumference will be measured horizontally at the level of the iliac crest with the patient in a standing position.[20]

### Disease activity

Disease activity will be measured by inflammatory markers CRP and ESR and with instruments according to IJD entity; Disease Activity Score-28 Calculator for RA

**Table 2** Data collection—clinical outcome measures

| Cardiopulmonary exercise test | | |
|---|---|---|
| **Outcome** | **Comment** | **Time point** |
| Forced expiratory volume (L) | Three attempts | Baseline, 3months, 6months |
| Forced vital capacity (L) | Three attempts | Baseline, 3months, 6months |
| Peak expiratory flow (L/min) | Three attempts | Baseline, 3months, 6months |
| Maximal voluntary ventilation (MVV, L/min) | Two attempts | Baseline, 3months, 6months |
| Peak oxygen uptake ($VO_{2peak}$, mL/kg/min and L/min) | | Baseline, 3months, 6months |
| Peak HR ($HR_{peak}$, beat/min) | Recorded at peak exercise | Baseline, 3months, 6months |
| Ventilatory threshold 1 | $VO_2$ (mL/kg/min) and HR are recorded | Baseline, 3months, 6months |
| Ventilatory threshold 2 | $VO_2$ (mL/kg/min/) and HR are recorded | Baseline, 3months, 6months |
| Maximum minute ventilation at peak exercise ($VE_{max}$, L/min) | | Baseline, 3months, 6months |
| Breathing reserve at peak exercise (%) | Difference between MVV and the maximum ventilation measured during CPET | Baseline, 3months, 6months |
| Oxygen pulse at peak exercise ($O_2$-pulse, mL/beat/min) | $VO_2$/HR, represents the product of stroke volume and the arterial-venous oxygen difference | Baseline, 3months, 6months |
| Ventilatory equivalent for oxygen ($V_E/VO_2$) | Ratio of the volume of gas expired per minute to $VO_2$ consumption per minute—registered at ventilatory threshold 1 and 2 | Baseline, 3months, 6months |
| Ventilatory equivalent for carbon dioxide ($V_E/VCO_2$) | Ratio of the volume of gas expired per minute to $VCO_2$ production per minute—registered at ventilatory threshold 1 and 2 | Baseline, 3months, 6months |
| Respiratory exchange ratio | $VCO_2/VO_2$, recorded at peak exercise | Baseline, 3months, 6months |
| Postexercise blood lactate concentration (mmol/L) | | Baseline, 3months, 6months |
| Borg RPE | At peak exercise, 0–10 | Baseline, 3months, 6months |
| **CVD risk factors** | | |
| **Outcome** | **Comment** | **Time point** |
| Blood samples<br>CRP (mg/L)<br>ESR (mm)<br>Total cholesterol (mmol/L)<br>HDL (mmol/L)<br>LDL (mmol/L)<br>Triglycerides (mmol/L) | Non-fasting | Baseline, 3 months, 6 months |
| Blood pressure and arterial stiffness<br>Systolic (mm Hg)<br>Diastolic (mm Hg)<br>Mean arterial pressure (mm Hg)<br>Resting HR (beat/min)<br>Augmentation index<br>Pulse wave velocity (m/s) | Supine | Baseline, 3 months, 6months |
| SCORE2 | | Baseline, 3months, 6months |
| **Anthropometric measures** | | |
| **Outcome** | **Comment** | **Time point** |
| Height (cm) | Nearest cm | Baseline, 3months, 6months |
| Body weight (kg) | Nearest 0.1 kg | Baseline, 3months, 6months |
| Waist circumference (cm) | Mean value of 2 measurements, nearest 0.5 cm | Baseline, 3months, 6months |
| Fat mass (kg) | Bioelectrical impedance analysis | Baseline, 3months, 6months |
| Fat-free mass (kg) | Bioelectrical impedance analysis | Baseline, 3months, 6months |
| Visceral fat indicator | Bioelectrical impedance analysis | Baseline, 3months, 6months |

Continued

Table 2 Continued

| Disease activity | | |
|---|---|---|
| **Outcome** | **Comment** | **Time point** |
| DAS28 | For patients presenting with RA<br>No of tender and swollen joints (out of 28), ESR or CRP and patient global assessment of health on a 100 mm Visual Analogue Scale | Baseline, 3months, 6months |
| DAPSA | For patients presenting with PsA<br>Numerical sum of tender joints (out of 68), swollen joints (out of 66), CRP and patient global assessment of disease activity and pain | Baseline, 3months, 6months |
| ASDAS | For patients presenting with SpA<br>Composite measure including patient-reported back pain, duration of morning stiffness, peripheral pain, patient global assessment and ESR or CRP | Baseline, 3months, 6months |

ASDAS, Ankylosing Spondylitis Disease Activity Score; Borg RPE, Borg rating of perceived exertion; CRP, C reactive protein; CVD, cardiovascular disease; DAPSA, Disease Activity Index for PSoriatic Arthritis; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; RPE, rating of perceived exertion; SCORE2, Systemic COronary Risk Estimation 2; $VCO_2$, volume of carbon dioxide; $V_E$, minute ventilation; $VO_2$, volume of oxygen.

(DAS28) is used as a measure of overall disease activity in patients presenting with RA,[41] Disease Activity Index for PSoriatic Arthritis (DAPSA) for patients with PsA[42] and Ankylosing Spondylitis Disease Activity Score (ASDAS) for patients with SpA.[43] Instrument-specific thresholds will be applied to provide categories of remission, low, moderate and high disease activity.

### Questionnaires

Prior to all study visits, patients will receive an email with link to an electronic questionnaire created with nettskjema.no, a survey solution developed and hosted by the University of Oslo (nettskjema@usit.uio.no). In cases where response to an electronic questionnaire is not feasible, a paper version will be supplied. The questionnaire includes personal background information, use of medication and healthcare services, pain, fatigue, disease activity, CVD symptoms, physical activity habits, exercise beliefs and self-efficacy of exercise. Questions regarding SARS-CoV-2 infection and/or quarantine, exercise behaviour and perceived change in physical fitness will be included at follow-up time points (table 3).

## Randomisation and allocation concealment

Following baseline assessments, patients are allocated 1:1 by a computer-generated randomisation schedule using permuted blocks of random sizes 4 and 6, stratified by gender. Project leader (ATT) is in charge of telephoning and assigning patients to designated group. The trial is single-blinded with outcome assessors (KRN and CF) blinded to group allocation. Patients and physiotherapists in charge of exercise sessions are not blinded to treatment exposure nor study hypothesis.

## Intervention

All patients, regardless of group allocation, will receive standard care following a consultation at the Preventive Cardio-Rheuma clinic, including CVD risk evaluation, lifestyle advice; heart-healthy diet, regular exercise, weight management and non-smoking given at baseline and prescription of relevant medication at the discretion of the attending physician.

### Intervention group (HIIT)

Patients randomised to the HIIT intervention group will be invited to receive a 12-week exercise intervention with 2 weekly HIIT exercise sessions guided by a physiotherapist at a primary care clinic. The initial 2 weeks of the intervention invites a progressive exercise load, starting from lower intensity and gradually increasing to a HIIT protocol. The HIIT protocol will include a 10 min warm-up, followed by 4×4 min at 90%–95% $HR_{peak}$, Borg RPE 16–18,[37] interspaced by 2–3 min active breaks at 60%–70% $HR_{peak,}$ Borg RPE 11–13. Uphill walking or running will be prioritised, but other modes of exercise, such as cycling or elliptical machine may also be used. Exercise work load will be tailored to each individual to provide the same relative exercise stress and to ensure progression.[28] Target exercise intensity will be monitored by a Polar H10 HR monitor (Polar, Kempele, Finland) connected to the training device or by wrist-based light sensors in Polar Ignite fitness watches (Polar, Kempele, Finland) provided to all HIIT participants. HR will be recorded in a training diary by the physiotherapist at the third minute of each interval bout with patients concurrently registering Borg RPE 6–20. The exercise programme will also include a recommendation for a third weekly, non-supervised exercise session at moderate intensity; 10 min warm-up at Borg RPE 11–12, followed by 30 min endurance exercise at Borg RPE 12–14. In these sessions, patients will be asked to record mean and maximum HR by use of Polar Ignite fitness watch as well as overall Borg RPE in the training diary.

**Table 3** Data collection from digital questionnaires

**Questions related to demographic variables and health**

| Topic | Measure | Time point |
|---|---|---|
| Demography | Relationship status<br>Education<br>Employment<br>Years diagnosed with IJD | Baseline |
| Health | Smoking and snuff use<br>Use of healthcare services the previous 3 months<br>CVD history<br>CVD symptoms<br>Use of medication; analgesics, IJD and CVD medication<br><br>SARS-CoV-2 infection and/or quarantine in the past 3 months | Baseline, 3months, 6months<br><br><br><br><br><br>3months, 6months |

**Questionnaires**

| Measure | Domains | Time point |
|---|---|---|
| Numeric Rating Scales of 0–10 | Pain during last week.<br>Fatigue during last week. | Baseline, 3months, 6months |
| EuroQol-5D-5L[57 58]* | Five domains with five response levels: Mobility, self-care, usual activities, pain/discomfort, anxiety/depression. | Baseline, 3months, 6months |
| EuroQol-5D-5L Visual Analogue Scale* | 0 (worst imaginable health)–100 (best imaginable health). | Baseline, 3months, 6months |
| Rheumatoid Arthritis Impact of Disease[59] | For patients presenting with RA<br>Seven domains: Pain, function, fatigue, physical and emotional well-being, sleep and coping. Domains are weighted, final score 0 (best)–10 (worst). | Baseline, 3months, 6months |
| Psoriatic Arthritis Impact of Disease[60] | For patients presenting with PsA<br>Nine domains: Pain, skin, fatigue, work/leisure, function, discomfort, sleep, anxiety, coping. Domains are weighted, final score 0 (best)–10 (worst). | Baseline, 3months, 6months |
| Bath Ankylosing Spondylitis Disease Activity Index[61] | For patients presenting with SpA<br>Six domains: Fatigue, axial pain, peripheral joint pain/swelling, pain at entheses, duration and severity of morning stiffness. Total score 0 (no disease activity)–10 (severe disease activity). | Baseline, 3months, 6months |
| Bath Ankylosing Spondylitis Functional Index[61] | For patients presenting with SpA<br>Ten activities scored from 0 (easy)–10 (impossible). Total score calculated as mean of all 10 domains. | Baseline, 3months, 6months |
| Bath Ankylosing Spondylitis Patient Global Score[61] | For patients presenting with SpA<br>Two questions (past week and past 6 months): Effect of disease on well-being ranked<br>0 (none)–10 (very severe). | Baseline, 3months, 6months |
| HUNT1 Physical Activity Questionnaire[62] | Three questions regarding exercise habits: Frequency, intensity and duration of exercise. | Baseline, 3months, 6months |
| Exercise beliefs and exercise habits[63] | Four subscales; self-efficacy for exercise (four elements), barriers to exercise (three elements), benefits of exercise (five elements), and impact of exercise on IJD (eight elements). Five-point Likert scale:<br>1 (strongly disagree)–5 (strongly agree). | Baseline, 3months, 6months |
| Change in physical fitness | 'To what degree has your level of physical fitness changed after entering the ExeHeart study?'<br>Five-point Likert scale:<br>1 (much better)–5 (much worse). | 3months, 6months |
| Acceptability and satisfaction with HIIT programme (self-developed for use in ExeHeart) | Only distributed to patients allocated to HIIT<br>14 domains related to experience with HIIT; intensity, frequency and duration of exercise sessions, social and physiotherapy support, motivation, effect, safety.<br>Five-point Likert scale:<br>1 (strongly disagree)–5 (strongly agree). | 3months |

Continued

Table 3 Continued

| Questionnaires | | |
|---|---|---|
| **Measure** | **Domains** | **Time point** |
| Self-reported frequency and mode of exercise | Three questions regarding participation in regular exercise the past 3 months (yes/no), frequency and mode of exercise | 3months (*control group participants only*), 6months (*all patients*) |
| COVID-19 infection and quarantine | Two questions regarding COVID-19 infection and/or quarantine during the past 3 months | 3months, 6months |

*Paper version of questionnaire is used, included at study visits with clinical assessments.
CVD, cardiovascular disease; HIIT, high-intensity training; HUNT, Trøndelag Health Study; IJD, Inflammatory joint disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis.

### Control group

Patients allocated to the control group will not be discouraged from taking part in regular exercise, but receive no targeted exercise intervention subsequent to baseline measurements. Succeeding the 6-month follow-up session, control group participants will be invited to attend an individual theoretical and practical HIIT session guided by a physiotherapist from the Norwegian National Unit for Rehabilitation for Rheumatic Patients with Special Needs.

### Adherence and tolerability

Adherence to HIIT will be recorded by use of the training diary. Exercise session attendance will be tallied and criteria for adherence is set to ≥70% (17/24) of HIIT sessions. HIIT exercise intensity sessions will be calculated as mean $\%HR_{peak}$ and Borg RPE 6-20 across sessions and participants. Likewise, duration will be reported as mean session duration and average time spent in high intensity intervals.[44] Tolerability of HIIT will be explored by clinical measures of disease activity with disease flares defined as increase in DAS28 >1.2 or>0.6 if DAS28 ≥3.2,[45] DAPSA≥7[46] or ASDAS≥0.9.[47]

At the 3-month point, an additional questionnaire will be distributed electronically to patients in the HIIT-group (n=*30*), addressing patients' acceptability and satisfaction with the HIIT programme (table 3). This questionnaire is self-developed in collaboration with the patient research partners. The ExeHeart trial will also include semi-structured interviews, targeting 5–7 patients in the intervention group. These interviews aim to explore barriers and facilitators in exercise adherence, experience with the HIIT protocol and perceived effects of exercise. The participants will be interviewed by a person unaffiliated to the research group.

### Patient safety and adverse events

Any abnormal values that are observed during clinical assessments throughout the study will be discussed with a cardiologist or rheumatologist as relevant. Patients eligible for inclusion will be examined by a cardiologist during the consultation at the Preventive Cardio-Rheuma clinic and further screened on contraindications to maximal exercise before entering the study.[20] The CPET will be supervised by physiotherapists (KRN or CF) that are trained in exercise physiology, have extensive knowledge of exercise stress tests and sufficient familiarity with indications to terminate a CPET.[48] In case of an adverse event, the hospital's emergency personnel will be alerted by alarm in accordance to hospital protocol.

Physiotherapists in primary care will be advised to use clinical checklists prior to each HIIT session; patient general well-being, absence of angina, dyspnoea or dizziness and resting HR <120. Furthermore, exercise sessions are to be ceased if HR does not increase with a higher workload or if the patient reports symptoms such as chest-pain or light-headedness.[49] Physiotherapists will be instructed to contact the patient's general practitioner and the project leader (ATT) in case of adverse events or abnormal exercise-related symptoms. Safety of HIIT will be monitored by asking patients and physiotherapists to record any events in the training diary.

## Data management

Encrypted data will be sent from nettskjema.no to Sensitive Data Services (TSD) at the University of Oslo, and downloaded to a secure server at Diakonhjemmet Hospital. Patients case report forms will be secured in locked cabinets according to hospital policy and will remain stored for 5 years after study completion. All data files will be stored in a secure research server at Diakonhjemmet Hospital with access to files restricted to project group members (KRN, HD, AGS, JSe, CF and ATT). Accuracy of data entry will be monitored by verification of a subset of data. Data may be shared on reasonable request to the project manager.

## Statistical analysis

The primary analysis will be a between group comparison of $VO_{2peak}$ (mL/kg/min). This will be carried out according to the intention-to-treat principle, and done by the analysis of covariance, adjusting for age, $VO_{2peak}$ values at baseline and other relevant factors. Secondary analyses will include between group comparisons on secondary outcomes, as well as comparisons in the per protocol population. Parametric and non-parametric statistical analyses will be carried out as appropriate based on visual inspection of variable distribution. No adjustment for multiple testing will be done.

The association between $VO_{2peak}$ and changes in disease activity and CVD risk factors will be assessed using multiple linear regression. The validity of eCRF models to accurately detect longitudinal change in $VO_{2peak}$ from baseline to follow-up will be assessed with Pearson or Spearman correlation and illustrated through Bland-Altman plot by comparing CPET-derived $VO_{2peak}$ to eCRF using an algorithm for the general population[19] and a model for RA populations.[50] Adherence, tolerability and acceptance of the HIIT protocol will be explored with descriptive statistics.

## Ethics and dissemination

The ExeHeart trial is evaluated and approved by the Regional Committee for Medical and Health Research Ethics (REC south-east 201227) and the Data Protection Officer at Diakonhjemmet Hospital (reg.no. 00397). Any protocol amendments are forwarded to REC and recorded in CinicalTrials.gov.

All procedures will be performed in adherence to the Helsinki declaration. Participants will be provided with written and oral information and asked to sign a consent form before enrolling in the study. No patients will, regardless of group allocation, receive treatment that falls short of standard clinical care. Possible risks that may impair study recruitment and follow-up are insecurities among patients regarding maximal exercise testing. We will assure patients that CPET is a safe procedure with very low risk of adverse events.[11] To reduce the risk of control group drop-out at repeated measures, we will invite control group participants to a physiotherapist-led theoretical and practical HIIT session following study close-out.

Dissemination of trial results will conform to Consolidated Standards of Reporting Trials guidelines[51] and Consensus on Exercise Reporting Template.[52] Results will be presented in international peer-reviewed, open access journals and through relevant communication platforms.

## Patient and public involvement

The ExeHeart trial is developed in agreement with Standard Protocol Items: Recommendations for Interventional Trials guidelines[53] and designed in collaboration with the Norwegian Rheumatism Association and patient research partners to enhance the relevance of research questions and feasibility of methods. Two experienced patient research partners from the Patient advisory board at Diakonhjemmet Hospital have been involved in the planning of ExeHeart and will contribute in all further phases of the trial.

# DISCUSSION

Despite compelling evidence of the potential of correctly dosed exercise in mitigating risk of disease, exercise is underutilized in CVD risk management in IJD.[21] We expect that the results of the ExeHeart trial will shed light on the effect and feasibility of HIIT in mitigating CVD risk in patients with IJD. If the results show favourable effects on CRF and few side effects, HIIT can be advocated as a safe and time-efficient mode of exercise for patients with IJD. Additionally, if eCRF models are deemed adequate in detecting change in CRF, future implementation of eCRF to clinical care may aid practitioners in accurately stratifying CVD risk.

Strengths of the study are the randomised controlled design, comprehensive clinical CVD risk assessments and blinding of outcome assessors. Furthermore, our trial is developed in close collaboration with patient research partners and aims to meet patient requests of effective, non-pharmacological treatment alternatives.

There are some limitations to our trial. Despite random allocation to HIIT, comparator contamination is plausible. Comprehensive health assessments, including a CPET, may reassure patients that exercise is safe and prompt physical behavioural changes to increased levels of physical activity.[54] Control group participants are not asked to refrain from physical activity and may enrol in exercise programmes outside of the study. The use of a sham exercise intervention for the control group was discussed, but deemed unsuitable in terms of use of resources in physiotherapy primary care.

Exercise intensity has emerged as a vital component of exercise programmes with compelling evidence of superior physiological adaptations following vigorous exercise. Indeed, a study in coronary heart disease reports superior effects in patients that exercise at the higher end of the HIIT intensity spectrum.[55] In our study, $HR_{peak}$ is derived from CPET and exercise intensity is measured as percentage of $HR_{peak}$ and Borg RPE 6–20. $HR_{peak}$ can deviate between repeated exercise tests and be underestimated in cases of peripheral fatigue.[34 49] Thus, we cannot rule out that using $HR_{peak}$ from a single CPET may lead to inaccurate prescription of HIIT HR zone.

Wearable fitness trackers have the potential to improve physical activity levels, especially in sedentary individuals.[56] In our trial, all patients in the HIIT group are provided with a personal fitness watch to monitor HR during exercise and further use of the fitness watch outside of exercise sessions is at the patient's preference. Feedback and cues from the fitness watch can potentially instigate physical activity behavioural changes that act in concert with the HIIT intervention.

In summary, ExeHeart is a pragmatic trial, aiming to generate applicable knowledge on the potential cardioprotective effect of HIIT in the context of IJD, the feasibility of HIIT in physiotherapy primary care and the validity of eCRF models.

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**Correction notice** This article has been has been corrected since it was first published. The figure 1 has been corrected.

**Acknowledgements** We thank the patients willing to participate in the ExeHeart trial and the Norwegian League against Rheumatism/Norwegian Rheumatism Association for collaboration in the planning of the study. Furthermore, we thank nurse Anne Stormyr Eirheim for training in measures of arterial stiffness and valuable help in patient enrollment. Lastly, we owe thanks to physiotherapist Henrik Gifstad at Atlet Fysio, physiotherapist Paal Drummond at Volvat and musculoskeletal physiotherapists Fred Hatlebrekke and Øyvind Eråas at Hans&Olaf Fysioterapi AS for their valuable enthusiasm and commitment in the ExeHeart trial.

**Contributors** KRN: study design, acquisition of data, drafting the article and final approval of the manuscript. AGS: study design, acquisition of data, critical revision and final approval of the manuscript. ATT, HD, JH, GSM, JSe, JSk, TB and KV: study design, critical revision and final approval of the manuscript. CF: acquisition of data, critical revision and final approval of the manuscript. No intended use of professional writers.

**Funding** This work is supported by the Dam foundation (grant number 2021/FO347439), Dr Trygve Gythfeldt and Wife research fund (June 2021, no grant number), the Norwegian Rheumatism Association (November 2021, no grant number) and the Norwegian Health Association (25576).

**Disclaimer** The funding sources have no role in the design, analysis and interpretation of the study.

**Competing interests** AGS has received lecture honoraria from AbbVie, Novartis, Bayer, Eli Lilly and Sanofi. AGS is secretary of ESC Cardiovascular Pharmacotherapy working group, nucleus member of EACP Risk Factor Management and Primary care and steering committee member for ATACC-RA, all gratuitous. GSM has received lecture honoraria from Novartis. JH has received lecture honoraria from Amgen. KRN, HD, KV, JSe, CF, JSk, TB and ATT have nothing to disclose.

**Patient consent for publication** Not applicable.

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



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Samtykke ExeHeart

Diakonhjemmet Sykehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

# ExeHeart- BEDRE HJERTE OG KARHELSE FOR PASIENTER MED INFLAMMATORISK LEDDSYKDOM

Dette er et spørsmål til deg om å delta i en forskningsstudie der målet er å undersøke tiltak som kan gi en bedre oppfølging av hjerte- og karhelse for deg som har inflammatorisk leddsykdom.

Pasienter med inflammatorisk leddsykdom har som følge av sin sykdom økt risiko for hjerte- og karsykdom. Til tross for dette er hjerte- og karsykdom underdiagnostisert og underbehandlet i denne pasientgruppen. Redusert fysisk form ($VO_{2peak}$) er en sterk og modifiserbar (noe man kan endre) risikofaktor for fremtidig hjerte-karsykdom. Høyintensiv kondisjonstrening kan øke den fysiske formen og potensielt forebygge hjerte-kar sykdom, samt fremme livskvalitet og mestring uten å medføre bivirkninger.

*Hensikten med studien* er å undersøke sammenheng og effekt av høyintensiv kondisjonstrening på fysisk form ($VO_{2peak}$), hjertekar-helse og sykdomsaktivitet hos pasienter med inflammatorisk leddsykdom. Treningen vil foregå på et fysikalsk institutt der vi også vil undersøke om pasienter og fysioterapeuter gjennomfører treningsprogrammet i henhold til protokollen. Videre vil vi undersøke om en enkel kondis-kalkulator er egnet til å fange opp endringer i fysisk form. I tillegg vil noen deltagere bli intervjuet med fokus på hvordan de har erfart en slik type trening.

Resultatet av studien kan gi verdifull informasjon om effekten av trening på risikofaktorer for hjerte- og karsykdom hos pasienter med inflammatorisk leddsykdom og om den type trening er mulig å gjennomføre i primærhelsetjenesten. Videre kan gyldigheten til kondis-kalkulator ha betydning for om slike målemetoder bør tas i bruk i klinisk praksis.

Vi ber om din deltakelse i prosjektet, så fremt du oppfyller følgende kriterier: Du må ha en inflammatorisk leddsykdom (revmatisk sykdom) som er diagnostisert av lege. I tillegg må du være i alderen 18-70 år og snakke norsk eller engelsk. Videre må du kunne gå sammenhengende i 15 minutter eller mer. Du kan ikke ha hatt operasjoner eller skader i ben/føtter i løpet av de 12 siste månedene. Du kan heller ikke delta dersom du har nevrologisk sykdom eller en hjerte-kar sykdom som innebærer at du ikke kan trene kondisjon med maksimal innsats. Dersom du har trent kondisjon med høy intensitet regelmessig 1 gang i uken eller mer de siste tre månedene, kan du ikke delta.

Diakonhjemmet sykehus er ansvarlig for studien.

## HVA INNEBÆRER PROSJEKTET?

Deltakelse i prosjektet innebærer at du gjennomfører undersøkelser på Diakonhjemmet sykehus tre ganger i løpet av ca 6 måneder. Etter den første runden med undersøkelser blir du trukket til å delta i treningsgruppe eller kontrollgruppe. Dersom du blir trukket ut til å delta i treningsgruppen, vil du få mulighet til å trene hos en fysioterapeut på et fysikalsk institutt i Oslo-området to ganger i uken i 12 uker. I tillegg ønsker vi at du etter fire uker også gjennomfører en treningsøkt på egenhånd hver uke. Treningen tilpasses til den enkelte og vil inneholde kondisjonstrening der du blir tydelig svett og andpusten. Hver treningsøkt varer i ca 45 minutter inkludert oppvarming og nedtrapping. Treningsøktene er lagt opp som intervalltrening- det vil si at du veksler mellom å jobbe med høy intensitet i 3-4 minutter og lav intensitet i 2-3 minutter. Treningen kan gjennomføres på sykkel, ellipsemaskin, gå i motbakke eller jogge/løpe.

Samtykke ExeHeart

Dersom du blir trukket til kontrollgruppe, vil du få standard behandling og oppfølging ved Diakonhjemmet sykehus. I tillegg vil du få tilbud om en veiledet treningsøkt hos fysioterapeut etter at prosjektet er gjennomført. Uavhengig av hvilken gruppe du havner i, vil du fortsette med vanlig oppfølging ved Revmatologisk poliklinikk og Forebyggende Hjerte-Revma klinikk.

**Følgende tester og undersøkelser gjennomføres ved start av studien:**

Som en del av undersøkelsen ved Diakonhjemmet vil det innhentes informasjon om undersøkelser du nylig har gjennomført ved Forebyggende Hjerte-Revma klinikk. Det gjelder informasjon fra spørreskjema om risikofaktorer for hjerte- og karsykdom, blodprøvesvar og resultat av undersøkelser (EKG, blodtrykk, måling av arteriell stivhet og ultralyd av halskar) som vil hentes ut fra din journal.

I tillegg vil du bli bedt om å gjennomgå:

*Spørreskjema* der du blir bedt om å oppgi informasjon om personlige forhold (alder, kjønn, utdannelse, arbeid, sivilstatus), treningsvaner samt barrierer og mestring av fysisk aktivitet. Du blir også bedt om å svare på spørsmål om bruk av helsetjenester, medikamentbruk, smerte, utmattelse, sykdomsaktivitet, sykdomsvarighet, fysisk funksjon, psykisk funksjon og mestring. Det er beregnet at det tar ca. 10-15 minutter å besvare spørreskjemaene.

*Undersøkelse av sykdomsaktivitet* der vi registrerer vonde og hovne ledd.

*Måling av vekt, høyde og midjeomkrets og kroppssammensetning.*

*Hvilepuls* som du måler selv om morgenen på testdagen. Hvilepuls vil også måles mens du ligger i ro på en benk.

*Test av lungefunksjon og fysisk form ($VO_{2peak}$)- CPET*
Først gjennomfører du pusteprøver for å måle lungefunksjon (spirometri). Deretter går du på tredemølle mens vi gradvis øker stigning og etter hvert hastighet. Testen tar vanligvis 8-12 minutter. Du puster gjennom en maske knyttet til et apparat som gir oss objektive mål på hvor hardt du tar i. På brystet har du lapper som er koblet til en EKG-maskin, slik at vi kan følge med på hjerterytmen din underveis. Du har også et blodtrykksapparat koblet med mansjett til en arm. Etter gjennomført test vil det bli tatt en liten blodprøve fra fingeren for å måle nivå av laktat (melkesyre) i blodet.

De siste 48 timene før kondisjonstest må du avstå fra all krevende fysisk aktivitet (trening) og alkohol. Koffeinholdig drikke og evt. røyk kan inntas frem til fire timer før test. De siste to timene før test av kondisjon bør du ikke spise, men du kan drikke vann.

**Følgende tester og undersøkelser gjennomføres etter 12 uker og 6 måneder:**

Ved oppfølging etter 12 uker og 6 måneder bes du ta blodprøver i forkant av konsultasjonen.

For øvrig vil du bli bedt om å gjennomgå de samme undersøkelsene *(sykdomsaktivitet, mål av vekt, høyde og midjeomkrets, kroppssammensetning, hvilepuls, blodtrykk, arteriell stivhet og test av fysisk form/CPET)* og svare på det samme spørreskjemaet som ved start av studien.

Etter fullført trening vil deltakere i treningsgruppen få tilsendt et spørreskjema der vi spør om hvordan treningen ble gjennomført og hvordan den enkelte deltaker opplevde treningen.

Samtykke ExeHeart

Vi vil gjennomføre intervjuer med noen av deltakerne i treningsgruppen. Hensikten med intervjuene er å undersøke faktorer som fremmet og hemmet gjennomføring av treningsprogrammet. Intervjuet vil foregå over fysisk eller som videokonsultasjon og vil vare i ca 45-60 minutter.

Alle opplysninger vil bli avidentifisert og behandlet konfidensielt. Det er kun de involverte i prosjektet som vil ha tilgang til opplysningene. Masterstudenter involvert i prosjektet vil kunne få tilgang til data gjennom Databehandleravtalen ved Diakonhjemmet sykehus.

## MULIGE FORDELER OG ULEMPER

Mange mosjonister ønsker i dag å undersøke sin fysiske form med hjelp av testene vi skal gjøre i dette prosjektet. Hvis du deltar i denne studien, vil du få objektiv informasjon om din fysiske form sammenliknet med den friske befolkningen, noe som kan hjelpe deg til videre treningsmotivasjon. Deltakelse i prosjektet vil kreve en del tid og oppmerksomhet. Test av fysisk form innebærer at du skal gå/løpe til utmattelse og vil oppleves som fysisk anstrengende. Blodprøven som tas i fingeren etter endt kondisjonstest vil oppleves som et lite stikk. Dersom du havner i treningsgruppen, vil du få veiledet trening hos en fysioterapeut i 12 uker. Dersom du havner i kontrollgruppen, vil du få tilbud om en time hos fysioterapeut etter at studien er avsluttet.

## FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Prosjektledere er professor Hanne Dagfinrud og seniorforsker Anne Therese Tveter. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte:

Prosjektmedarbeider og PhD stipendiat Kristine Røren Nordén, mail: kristineroren.norden@diakonsyk.no, tlf: 92043801.

Seniorforsker Anne Therese Tveter, mail: annetherese.tveter@diakonsyk.no, tlf: 91115550

## HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Alle som får innsyn i informasjonen om deg har taushetsplikt. Resultatene fra studien vil offentliggjøres i internasjonale, fagfellevurderte tidsskrift. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Du vil få tilsendt artiklene dersom du ønsker det.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet, og planlegges brukt til 2029. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra regional etiske komité og andre relevante myndigheter.

Samtykke ExeHeart

## FORSIKRING

Deltakere i studien er forsikret gjennom pasientskadeloven.

## GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, REK ref.nr 201227.

## SAMTYKKE TIL DELTAKELSE I PROSJEKTET

Hvis du ønsker å delta i prosjektet ber vi deg underskrive og oppi telefonnummer på vedlagt samtykkeskjema.

## JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Jeg har lest informasjonsskrivet og samtykker til å delta i forskningsprosjektet.

**Signatur:**

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**Sted og dato:**

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**Fornavn** (blokkbokstaver)**:**

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**Etternavn** (blokkbokstaver)**:**

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**Mobiltelefonnummer:**

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**Epost adresse:**

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☐ Jeg godtar å bli kontaktet for deltagelse i intervju etter fullført treningsintervensjon. *(Du kan delta i ExeHeart selv om du ikke deltar i intervjuene)*

Jeg bekrefter å ha gitt informasjon om prosjektet

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Sted og dato

Signatur

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Rolle i prosjektet

ExeHeart Patient Consent Form

Diakonhjemmet Sykehus

## INFORMED CONSENT FORM FOR THE RESEARCH PROJECT

# ExeHeart- IMPROVED CARDIOVACULAR HEALTH FOR PATIENTS WITH INFLAMMATORY JOINT DISEASE

This is an invitation to participate in a research study where the purpose is to investigate measures that can improve cardiovascular health management for patients presenting with inflammatory joint disease.

Patients with inflammatory joint disease have an increased risk of cardiovascular disease. Despite this knowledge, cardiovascular disease is underdiagnosed and undertreated in this patient group. Reduced physical fitness (VO2peak) is a strong and modifiable (something that can be changed) risk factor for future cardiovascular disease. High-intensity exercise can increase physical fitness and potentially prevent cardiovascular disease, as well as promote quality of life and coping without harmful side effects.

The purpose of this study is to investigate the association and effect of high-intensity interval exercise on physical fitness (VO2peak), cardiovascular health and disease activity in patients with inflammatory joint disease. The exercise will be supervised by physiotherapists in primary care and we aim to assess if patients and physiotherapists are able to complete the exercise program in accordance with the protocol. Furthermore, we will investigate whether a simple fitness calculator is suitable to detect change in physical fitness. Additionally, some participants will be invited to participate in interviews focusing on individual experience in participating in the study and exercise program.

Results from the study can provide valuable information regarding the effect of exercise on cardiovascular disease risk factors risk factors in patients with inflammatory joint disease and whether this mode of exercise is feasible in a primary health care setting. Furthermore, exploring the validity of the fitness calculator may impact how fitness calculators can be used in clinical practice.

We invite you to participate in the project should you meet the following criteria: You have an inflammatory joint disease (rheumatic disease) that has been diagnosed by a physician. Additionally, you are 18-70 years old and speak Norwegian or English. Furthermore, you must be able to walk continuously for 15 minutes or more. You cannot have sustained surgery or injuries to your legs / feet during the last 12 months. You can't participate if you have a neurological disease or a cardiovascular disease where exercise at maximum effort is discouraged. Should you already exercise regularly high intensity regularly (once a week or more) and have been doing so for the past three months, you will not be able to participate in the study.

Diakonhjemmet hospital is the responsible institution for the study.

## WHAT DOES PARTICIPATION ENTAIL?

If you consent to participate in the study, you will be invited to three individual consultations at Diakonhjemmet hospital over the course of 6 months. After the first consultation, you will be randomly allocated to the exercise group or the control group. If you are allocated to the exercise group, you will have the opportunity to exercise two times per week for 12 weeks with supervision from a physiotherapist at a primary care clinic in the municipality of Oslo. Furthermore, after the first four weeks, we recommend you to include an additional non-supervised weekly exercise session. The exercise program will be individually tailored and will include endurance exercise at an intensity where you will be out of breath and perspiring. Duration of workout sessions is roughly 45 minutes including warm-up and cool-down. The exercise sessions are designed as interval training - that is, you alternate between bouts of high intensity for 3-4 minutes interspaced with bouts if low intensity for 2-3 minutes. The exercise may be done on a bicycle, elliptical machine, walking uphill or jogging / running.

ExeHeart Patient Consent Form

If you are allocated to the control group, you will receive standard treatment and follow-up at Diakonhjemmet hospital. Additionally, you will be offered a guided exercise session with a physiotherapist after your 6-month follow-up session. Regardless of group allocation, you will continue with regular follow-up at the Rheumatology outpatient clinic and the Preventive Cardio-Rheuma clinic.

**Study procedures at the start of the study:**

As part of the first study consultation at Diakonhjemmet hospital, information will be obtained from your recent examination at the Preventive Cardio-Rheuma clinic. This includes information from your medical record regarding a questionnaire on cardiovascular disease risk factors, blood samples and clinical examinations (ECG, blood pressure, measurement of arterial stiffness and ultrasound of the carotid arteries).

Furthermore, you will be asked to complete:

*Questionnaire* regarding personal information (age, gender, education, work, marital status), exercise habits as well as barriers and facilitators to physical activity. You will be asked questions regarding use of healthcare services, medication, pain, fatigue, disease activity, disease duration, physical function, psychological function and coping. We estimate that you will spend approx. 10-15 minutes to answer the questionnaires.

*Measure of disease activity* where we register tender and swollen joints.

*Measurement of weight, height, waist circumference and body composition*.

*Resting heart rate* that you measure in the morning prior to your consultation. Resting heart rate will also be measured during the consultation at Diakonhjemmet hospital.

*Lung function and physical fitness (VO2peak) - CPET*
First, you will be asked to perform tests of pulmonary function/breathing tests (spirometry) to measure the amount of air you can breathe in and out of your lungs, as well as how fast you can the blow the air out of your lungs. Next, you are asked to talk on the treadmill with gradual increase of speed and inclination until you reach exhaustion. This test usually takes 8-12 minutes. You breathe through a mask attached to a device that allows us to collect information on your level of exertion. Electrodes attached to the skin on your chest allows us to measure the electrical activity of your heart during the treadmill test. A blood pressure monitor connected is connected to one arm and blood pressure is measured at regular intervals during the treadmill test. After completing the treadmill test, a small blood sample will be taken from the pulpa of one finger to assess the level of lactate (lactic acid) in your blood.

You are asked to refrain from all demanding physical activity (exercise) and alcohol the last 48 hours before the treadmill test. Caffeinated beverages and nicotine can be consumed up to four hours before the test. You are asked to refrain from eating the last two hours leading up to the treadmill test, but you may drink water.

**Study procedures at 12 weeks and 6 months:**

At 12-week and 6-month follow-up, you will be asked to take blood samples at Diakonhjemmet hospital prior to the clinical consultation.

Furthermore, you are invited to complete the same examinations (disease activity, measurements of weight, height and waist circumference, body composition, resting heart rate, blood pressure, arterial stiffness and test of physical fitness / CPET) and answer the same questionnaire as at the start of the study .

ExeHeart Patient Consent Form

After completing the exercise training, participants in the exercise group will be forwarded a questionnaire with questions on how the exercise was carried out and how the individual participant experienced the exercise program.

We will conduct interviews with some of the participants in the exercise group. The purpose of the interviews is to examine possible barriers and facilitators to implementation of the exercise program. The duration of interviews is estimated to 45-60 minutes and the interviews will be done face-to-face or as a video consultation.

All information will be de-identified and treated confidentially. Only those involved in the project will have access to the information. Master students affiliated to the project will be able to access data through the Data Processor Agreement at Diakonhjemmet Hospital.

## BENEFITS AND RISKS

Many individuals want to assess their physical fitness with tests that we use in this research project. Should you consent to participate, you will receive information regarding your physical fitness and how your individual fitness compares to reference values from a healthy population. This may help you in your future motivation for exercise. Participating in the study will entail time and attention on your part. Physical fitness tests involve walking/running to a level of exhaustion and will and will be perceived as physically strenuous. The blood sample taken from a finger after completing the fitness test will be experienced as a small sting. If you are allocated to the exercise group, you will receive supervised training from a physiotherapist for 12 weeks. If you are allocated to the control group, you will be offered an individual consultation with a physiotherapist after completing all study visits.

ExeHeart Patient Consent Form

## VOLUNTARY PARTICIPATION

Participation in the study is voluntary. Should you choose to participate, please sign the declaration of consent on the last page. You can withdraw your consent at any time without giving any reason. This will not have any consequences for your further treatment. If you withdraw from the project, you can request that all your collected data and information be deleted, unless the information has already been included in data analysis or used in scientific publications. Project managers are Professor Hanne Dagfinrud and senior researcher Anne Therese Tveter. Contact information for withdrawal of consent or any other questions regarding the project:

Principal investigator and PhD fellow Kristine Røren Nordén, email: kristineroren.norden@diakonsyk.no, tel: 92043801.

Senior researcher Anne Therese Tveter, email: annetherese.tveter@diakonsyk.no, tel: 91115550

## CONFIDENTIALITY

All collected data and information may only be used as described in the purpose of the study. You have the right to access the information that is registered about you and to have any errors in the information corrected.

All information will be processed without name and birth number or other identifiable information. A code list links you to your information by a name list. Everyone that has access to study files have a duty of confidentiality. Study results will be published in international, peer-reviewed journals. All data will be anonymized and no study participants will be identifiable in the published results. You will be forwarded the articles at your request.

The project manager is responsible for the day-to-day running of the study and oversees that all information and data are processed in a secure manner. The information registered about you should only be used as described in purpose of the project, and may be used until 2029. Any time extensions for use and storage can only take place after approval from the regional ethics committee and other relevant authorities.

## INSURANCE

Participants in the study are insured through the Patient Injuries Act.

## APPROVAL

The project has been approved by the Regional Committee for Medical and Health Research Ethics, REK ref. No. 201227.

# CONSENT TO PARTICIPATION IN THE PROJECT

If you consent to participate in the project, we ask you to sign and enter the telephone number on the enclosed consent form.

## I CONSENT TO PARTICIPATE IN THE PROJECT

I have read the information letter and consent to participate in the research project.

**Signature:** **Place and date:**

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**First name (block letters):** **Surname (block letters):**

ExeHeart Patient Consent Form

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**Mobile phone number:**

**E-mail address:**

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☐ I consent to be contacted for participation in the interview after completing the training intervention. (You can participate in ExeHeart even if you do not participate in the interviews)

I confirm that I have provided information about the project

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Place and date

Signature

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Project affiliation

Samtykke ExeHeart

Diakonhjemmet Sykehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

# ExeHeart- BEDRE HJERTE OG KARHELSE FOR PASIENTER MED INFLAMMATORISK LEDDSYKDOM

Dette er et spørsmål til deg om å delta i en forskningsstudie der målet er å undersøke tiltak som kan gi en bedre oppfølging av hjerte- og karhelse for deg som har inflammatorisk leddsykdom.

Pasienter med inflammatorisk leddsykdom har som følge av sin sykdom økt risiko for hjerte- og karsykdom. Til tross for dette er hjerte- og karsykdom underdiagnostisert og underbehandlet i denne pasientgruppen. Redusert fysisk form ($VO_{2peak}$) er en sterk og modifiserbar (noe man kan endre) risikofaktor for fremtidig hjerte-karsykdom. Høyintensiv kondisjonstrening kan øke den fysiske formen og potensielt forebygge hjerte-kar sykdom, samt fremme livskvalitet og mestring uten å medføre bivirkninger.

*Hensikten med studien* er å undersøke sammenheng og effekt av høyintensiv kondisjonstrening på fysisk form ($VO_{2peak}$), hjertekar-helse og sykdomsaktivitet hos pasienter med inflammatorisk leddsykdom. Treningen vil foregå på et fysikalsk institutt der vi også vil undersøke om pasienter og fysioterapeuter gjennomfører treningsprogrammet i henhold til protokollen. Videre vil vi undersøke om en enkel kondis-kalkulator er egnet til å fange opp endringer i fysisk form. I tillegg vil noen deltagere bli intervjuet med fokus på hvordan de har erfart en slik type trening.

Resultatet av studien kan gi verdifull informasjon om effekten av trening på risikofaktorer for hjerte- og karsykdom hos pasienter med inflammatorisk leddsykdom og om den type trening er mulig å gjennomføre i primærhelsetjenesten. Videre kan gyldigheten til kondis-kalkulator ha betydning for om slike målemetoder bør tas i bruk i klinisk praksis.

Vi ber om din deltakelse i prosjektet, så fremt du oppfyller følgende kriterier: Du må ha en inflammatorisk leddsykdom (revmatisk sykdom) som er diagnostisert av lege. I tillegg må du være i alderen 18-70 år og snakke norsk eller engelsk. Videre må du kunne gå sammenhengende i 15 minutter eller mer. Du kan ikke ha hatt operasjoner eller skader i ben/føtter i løpet av de 12 siste månedene. Du kan heller ikke delta dersom du har nevrologisk sykdom eller en hjerte-kar sykdom som innebærer at du ikke kan trene kondisjon med maksimal innsats. Dersom du har trent kondisjon med høy intensitet regelmessig 1 gang i uken eller mer de siste tre månedene, kan du ikke delta.

Diakonhjemmet sykehus er ansvarlig for studien.

## HVA INNEBÆRER PROSJEKTET?

Deltakelse i prosjektet innebærer at du gjennomfører undersøkelser på Diakonhjemmet sykehus tre ganger i løpet av ca 6 måneder. Etter den første runden med undersøkelser blir du trukket til å delta i treningsgruppe eller kontrollgruppe. Dersom du blir trukket ut til å delta i treningsgruppen, vil du få mulighet til å trene hos en fysioterapeut på et fysikalsk institutt i Oslo-området to ganger i uken i 12 uker. I tillegg ønsker vi at du etter fire uker også gjennomfører en treningsøkt på egenhånd hver uke. Treningen tilpasses til den enkelte og vil inneholde kondisjonstrening der du blir tydelig svett og andpusten. Hver treningsøkt varer i ca 45 minutter inkludert oppvarming og nedtrapping. Treningsøktene er lagt opp som intervalltrening- det vil si at du veksler mellom å jobbe med høy intensitet i 3-4 minutter og lav intensitet i 2-3 minutter. Treningen kan gjennomføres på sykkel, ellipsemaskin, gå i motbakke eller jogge/løpe.

Samtykke ExeHeart

Dersom du blir trukket til kontrollgruppe, vil du få standard behandling og oppfølging ved Diakonhjemmet sykehus. I tillegg vil du få tilbud om en veiledet treningsøkt hos fysioterapeut etter at prosjektet er gjennomført. Uavhengig av hvilken gruppe du havner i, vil du fortsette med vanlig oppfølging ved Revmatologisk poliklinikk og Forebyggende Hjerte-Revma klinikk.

**Følgende tester og undersøkelser gjennomføres ved start av studien:**

Som en del av undersøkelsen ved Diakonhjemmet vil det innhentes informasjon om undersøkelser du nylig har gjennomført ved Forebyggende Hjerte-Revma klinikk. Det gjelder informasjon fra spørreskjema om risikofaktorer for hjerte- og karsykdom, blodprøvesvar og resultat av undersøkelser (EKG, blodtrykk, måling av arteriell stivhet og ultralyd av halskar) som vil hentes ut fra din journal.

I tillegg vil du bli bedt om å gjennomgå:

*Spørreskjema* der du blir bedt om å oppgi informasjon om personlige forhold (alder, kjønn, utdannelse, arbeid, sivilstatus), treningsvaner samt barrierer og mestring av fysisk aktivitet. Du blir også bedt om å svare på spørsmål om bruk av helsetjenester, medikamentbruk, smerte, utmattelse, sykdomsaktivitet, sykdomsvarighet, fysisk funksjon, psykisk funksjon og mestring. Det er beregnet at det tar ca. 10-15 minutter å besvare spørreskjemaene.

*Undersøkelse av sykdomsaktivitet* der vi registrerer vonde og hovne ledd.

*Måling av vekt, høyde og midjeomkrets og kroppssammensetning.*

*Hvilepuls* som du måler selv om morgenen på testdagen. Hvilepuls vil også måles mens du ligger i ro på en benk.

*Test av lungefunksjon og fysisk form ($VO_{2peak}$)- CPET*
Først gjennomfører du pusteprøver for å måle lungefunksjon (spirometri). Deretter går du på tredemølle mens vi gradvis øker stigning og etter hvert hastighet. Testen tar vanligvis 8-12 minutter. Du puster gjennom en maske knyttet til et apparat som gir oss objektive mål på hvor hardt du tar i. På brystet har du lapper som er koblet til en EKG-maskin, slik at vi kan følge med på hjerterytmen din underveis. Du har også et blodtrykksapparat koblet med mansjett til en arm. Etter gjennomført test vil det bli tatt en liten blodprøve fra fingeren for å måle nivå av laktat (melkesyre) i blodet.

De siste 48 timene før kondisjonstest må du avstå fra all krevende fysisk aktivitet (trening) og alkohol. Koffeinholdig drikke og evt. røyk kan inntas frem til fire timer før test. De siste to timene før test av kondisjon bør du ikke spise, men du kan drikke vann.

**Følgende tester og undersøkelser gjennomføres etter 12 uker og 6 måneder:**

Ved oppfølging etter 12 uker og 6 måneder bes du ta blodprøver i forkant av konsultasjonen.

For øvrig vil du bli bedt om å gjennomgå de samme undersøkelsene *(sykdomsaktivitet, mål av vekt, høyde og midjeomkrets, kroppssammensetning, hvilepuls, blodtrykk, arteriell stivhet og test av fysisk form/CPET)* og svare på det samme spørreskjemaet som ved start av studien.

Etter fullført trening vil deltakere i treningsgruppen få tilsendt et spørreskjema der vi spør om hvordan treningen ble gjennomført og hvordan den enkelte deltaker opplevde treningen.

Samtykke ExeHeart

Vi vil gjennomføre intervjuer med noen av deltakerne i treningsgruppen. Hensikten med intervjuene er å undersøke faktorer som fremmet og hemmet gjennomføring av treningsprogrammet. Intervjuet vil foregå over fysisk eller som videokonsultasjon og vil vare i ca 45-60 minutter.

Alle opplysninger vil bli avidentifisert og behandlet konfidensielt. Det er kun de involverte i prosjektet som vil ha tilgang til opplysningene. Masterstudenter involvert i prosjektet vil kunne få tilgang til data gjennom Databehandleravtalen ved Diakonhjemmet sykehus.

## MULIGE FORDELER OG ULEMPER

Mange mosjonister ønsker i dag å undersøke sin fysiske form med hjelp av testene vi skal gjøre i dette prosjektet. Hvis du deltar i denne studien, vil du få objektiv informasjon om din fysiske form sammenliknet med den friske befolkningen, noe som kan hjelpe deg til videre treningsmotivasjon. Deltakelse i prosjektet vil kreve en del tid og oppmerksomhet. Test av fysisk form innebærer at du skal gå/løpe til utmattelse og vil oppleves som fysisk anstrengende. Blodprøven som tas i fingeren etter endt kondisjonstest vil oppleves som et lite stikk. Dersom du havner i treningsgruppen, vil du få veiledet trening hos en fysioterapeut i 12 uker. Dersom du havner i kontrollgruppen, vil du få tilbud om en time hos fysioterapeut etter at studien er avsluttet.

## FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Prosjektledere er professor Hanne Dagfinrud og seniorforsker Anne Therese Tveter. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte:

Prosjektmedarbeider og PhD stipendiat Kristine Røren Nordén, mail: kristineroren.norden@diakonsyk.no, tlf: 92043801.

Seniorforsker Anne Therese Tveter, mail: annetherese.tveter@diakonsyk.no, tlf: 91115550

## HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Alle som får innsyn i informasjonen om deg har taushetsplikt. Resultatene fra studien vil offentliggjøres i internasjonale, fagfellevurderte tidsskrift. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Du vil få tilsendt artiklene dersom du ønsker det.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet, og planlegges brukt til 2029. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra regional etiske komité og andre relevante myndigheter.

Samtykke ExeHeart

## FORSIKRING

Deltakere i studien er forsikret gjennom pasientskadeloven.

## GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, REK ref.nr 201227.

## SAMTYKKE TIL DELTAKELSE I PROSJEKTET

Hvis du ønsker å delta i prosjektet ber vi deg underskrive og oppi telefonnummer på vedlagt samtykkeskjema.

## JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Jeg har lest informasjonsskrivet og samtykker til å delta i forskningsprosjektet.

**Signatur:**

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**Sted og dato:**

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**Fornavn** (blokkbokstaver)**:**

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**Etternavn** (blokkbokstaver)**:**

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**Mobiltelefonnummer:**

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**Epost adresse:**

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☐ Jeg godtar å bli kontaktet for deltagelse i intervju etter fullført treningsintervensjon. *(Du kan delta i ExeHeart selv om du ikke deltar i intervjuene)*

Jeg bekrefter å ha gitt informasjon om prosjektet

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Sted og dato

Signatur

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Rolle i prosjektet

ExeHeart Patient Consent Form

Diakonhjemmet Sykehus

## INFORMED CONSENT FORM FOR THE RESEARCH PROJECT

# ExeHeart- IMPROVED CARDIOVACULAR HEALTH FOR PATIENTS WITH INFLAMMATORY JOINT DISEASE

This is an invitation to participate in a research study where the purpose is to investigate measures that can improve cardiovascular health management for patients presenting with inflammatory joint disease.

Patients with inflammatory joint disease have an increased risk of cardiovascular disease. Despite this knowledge, cardiovascular disease is underdiagnosed and undertreated in this patient group. Reduced physical fitness (VO2peak) is a strong and modifiable (something that can be changed) risk factor for future cardiovascular disease. High-intensity exercise can increase physical fitness and potentially prevent cardiovascular disease, as well as promote quality of life and coping without harmful side effects.

The purpose of this study is to investigate the association and effect of high-intensity interval exercise on physical fitness (VO2peak), cardiovascular health and disease activity in patients with inflammatory joint disease. The exercise will be supervised by physiotherapists in primary care and we aim to assess if patients and physiotherapists are able to complete the exercise program in accordance with the protocol. Furthermore, we will investigate whether a simple fitness calculator is suitable to detect change in physical fitness. Additionally, some participants will be invited to participate in interviews focusing on individual experience in participating in the study and exercise program.

Results from the study can provide valuable information regarding the effect of exercise on cardiovascular disease risk factors risk factors in patients with inflammatory joint disease and whether this mode of exercise is feasible in a primary health care setting. Furthermore, exploring the validity of the fitness calculator may impact how fitness calculators can be used in clinical practice.

We invite you to participate in the project should you meet the following criteria: You have an inflammatory joint disease (rheumatic disease) that has been diagnosed by a physician. Additionally, you are 18-70 years old and speak Norwegian or English. Furthermore, you must be able to walk continuously for 15 minutes or more. You cannot have sustained surgery or injuries to your legs / feet during the last 12 months. You can't participate if you have a neurological disease or a cardiovascular disease where exercise at maximum effort is discouraged. Should you already exercise regularly high intensity regularly (once a week or more) and have been doing so for the past three months, you will not be able to participate in the study.

Diakonhjemmet hospital is the responsible institution for the study.

## WHAT DOES PARTICIPATION ENTAIL?

If you consent to participate in the study, you will be invited to three individual consultations at Diakonhjemmet hospital over the course of 6 months. After the first consultation, you will be randomly allocated to the exercise group or the control group. If you are allocated to the exercise group, you will have the opportunity to exercise two times per week for 12 weeks with supervision from a physiotherapist at a primary care clinic in the municipality of Oslo. Furthermore, after the first four weeks, we recommend you to include an additional non-supervised weekly exercise session. The exercise program will be individually tailored and will include endurance exercise at an intensity where you will be out of breath and perspiring. Duration of workout sessions is roughly 45 minutes including warm-up and cool-down. The exercise sessions are designed as interval training - that is, you alternate between bouts of high intensity for 3-4 minutes interspaced with bouts if low intensity for 2-3 minutes. The exercise may be done on a bicycle, elliptical machine, walking uphill or jogging / running.

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If you are allocated to the control group, you will receive standard treatment and follow-up at Diakonhjemmet hospital. Additionally, you will be offered a guided exercise session with a physiotherapist after your 6-month follow-up session. Regardless of group allocation, you will continue with regular follow-up at the Rheumatology outpatient clinic and the Preventive Cardio-Rheuma clinic.

**Study procedures at the start of the study:**

As part of the first study consultation at Diakonhjemmet hospital, information will be obtained from your recent examination at the Preventive Cardio-Rheuma clinic. This includes information from your medical record regarding a questionnaire on cardiovascular disease risk factors, blood samples and clinical examinations (ECG, blood pressure, measurement of arterial stiffness and ultrasound of the carotid arteries).

Furthermore, you will be asked to complete:

*Questionnaire* regarding personal information (age, gender, education, work, marital status), exercise habits as well as barriers and facilitators to physical activity. You will be asked questions regarding use of healthcare services, medication, pain, fatigue, disease activity, disease duration, physical function, psychological function and coping. We estimate that you will spend approx. 10-15 minutes to answer the questionnaires.

*Measure of disease activity* where we register tender and swollen joints.

*Measurement of weight, height, waist circumference and body composition*.

*Resting heart rate* that you measure in the morning prior to your consultation. Resting heart rate will also be measured during the consultation at Diakonhjemmet hospital.

*Lung function and physical fitness (VO2peak) - CPET*
First, you will be asked to perform tests of pulmonary function/breathing tests (spirometry) to measure the amount of air you can breathe in and out of your lungs, as well as how fast you can the blow the air out of your lungs. Next, you are asked to talk on the treadmill with gradual increase of speed and inclination until you reach exhaustion. This test usually takes 8-12 minutes. You breathe through a mask attached to a device that allows us to collect information on your level of exertion. Electrodes attached to the skin on your chest allows us to measure the electrical activity of your heart during the treadmill test. A blood pressure monitor connected is connected to one arm and blood pressure is measured at regular intervals during the treadmill test. After completing the treadmill test, a small blood sample will be taken from the pulpa of one finger to assess the level of lactate (lactic acid) in your blood.

You are asked to refrain from all demanding physical activity (exercise) and alcohol the last 48 hours before the treadmill test. Caffeinated beverages and nicotine can be consumed up to four hours before the test. You are asked to refrain from eating the last two hours leading up to the treadmill test, but you may drink water.

**Study procedures at 12 weeks and 6 months:**

At 12-week and 6-month follow-up, you will be asked to take blood samples at Diakonhjemmet hospital prior to the clinical consultation.

Furthermore, you are invited to complete the same examinations (disease activity, measurements of weight, height and waist circumference, body composition, resting heart rate, blood pressure, arterial stiffness and test of physical fitness / CPET) and answer the same questionnaire as at the start of the study .

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After completing the exercise training, participants in the exercise group will be forwarded a questionnaire with questions on how the exercise was carried out and how the individual participant experienced the exercise program.

We will conduct interviews with some of the participants in the exercise group. The purpose of the interviews is to examine possible barriers and facilitators to implementation of the exercise program. The duration of interviews is estimated to 45-60 minutes and the interviews will be done face-to-face or as a video consultation.

All information will be de-identified and treated confidentially. Only those involved in the project will have access to the information. Master students affiliated to the project will be able to access data through the Data Processor Agreement at Diakonhjemmet Hospital.

## BENEFITS AND RISKS

Many individuals want to assess their physical fitness with tests that we use in this research project. Should you consent to participate, you will receive information regarding your physical fitness and how your individual fitness compares to reference values from a healthy population. This may help you in your future motivation for exercise. Participating in the study will entail time and attention on your part. Physical fitness tests involve walking/running to a level of exhaustion and will and will be perceived as physically strenuous. The blood sample taken from a finger after completing the fitness test will be experienced as a small sting. If you are allocated to the exercise group, you will receive supervised training from a physiotherapist for 12 weeks. If you are allocated to the control group, you will be offered an individual consultation with a physiotherapist after completing all study visits.

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## VOLUNTARY PARTICIPATION

Participation in the study is voluntary. Should you choose to participate, please sign the declaration of consent on the last page. You can withdraw your consent at any time without giving any reason. This will not have any consequences for your further treatment. If you withdraw from the project, you can request that all your collected data and information be deleted, unless the information has already been included in data analysis or used in scientific publications. Project managers are Professor Hanne Dagfinrud and senior researcher Anne Therese Tveter. Contact information for withdrawal of consent or any other questions regarding the project:

Principal investigator and PhD fellow Kristine Røren Nordén, email: kristineroren.norden@diakonsyk.no, tel: 92043801.

Senior researcher Anne Therese Tveter, email: annetherese.tveter@diakonsyk.no, tel: 91115550

## CONFIDENTIALITY

All collected data and information may only be used as described in the purpose of the study. You have the right to access the information that is registered about you and to have any errors in the information corrected.

All information will be processed without name and birth number or other identifiable information. A code list links you to your information by a name list. Everyone that has access to study files have a duty of confidentiality. Study results will be published in international, peer-reviewed journals. All data will be anonymized and no study participants will be identifiable in the published results. You will be forwarded the articles at your request.

The project manager is responsible for the day-to-day running of the study and oversees that all information and data are processed in a secure manner. The information registered about you should only be used as described in purpose of the project, and may be used until 2029. Any time extensions for use and storage can only take place after approval from the regional ethics committee and other relevant authorities.

## INSURANCE

Participants in the study are insured through the Patient Injuries Act.

## APPROVAL

The project has been approved by the Regional Committee for Medical and Health Research Ethics, REK ref. No. 201227.

# CONSENT TO PARTICIPATION IN THE PROJECT

If you consent to participate in the project, we ask you to sign and enter the telephone number on the enclosed consent form.

## I CONSENT TO PARTICIPATE IN THE PROJECT

I have read the information letter and consent to participate in the research project.

**Signature:** **Place and date:**

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**First name (block letters):** **Surname (block letters):**

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**Mobile phone number:**

**E-mail address:**

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☐ I consent to be contacted for participation in the interview after completing the training intervention. (You can participate in ExeHeart even if you do not participate in the interviews)

I confirm that I have provided information about the project

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Place and date

Signature

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Project affiliation