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BMJ Open

Effect of a 12-week high-intensity exercise intervention: a comparison of cardiac exercise adaptations during biological disease-modifying antirheumatic drug treatment (TNF inhibitors vs IL-6 signalling inhibitors) in patients with rheumatoid arthritis – study protocol for a randomised controlled trial

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ABSTRACT

Introduction The chronic inflammatory state in rheumatoid arthritis (RA) augments the risk of cardiovascular disease (CVD), with pro-inflammatory cytokines tumour necrosis factor (TNF) and interleukin 6 (IL-6) playing a vital role. Consequently, biological disease-modifying antirheumatic drugs (bDMARDs) may attenuate that risk. IL-6 is also a myokine, secreted from exercising skeletal muscles, where IL-6 exhibits anti-inflammatory effects that may ameliorate the risk of CVD. In healthy humans treated with IL-6 signalling inhibitors (IL-6i), exercise induced loss of visceral fat mass and cardiac adaptations were abolished. We hypothesise that IL-6 signalling inhibition will impair the cardiac and metabolic adaptions to exercise training compared with TNF inhibition in RA patients.

Methods and analysis 80 RA patients treated with IL-6i (n=40) or TNF inhibitors (n=40) are included in a 12-week randomised investigator-blinded 4×4 min high-intensity interval training (HIIT) study. Patients are stratified for medical treatment and sex and allocated 1:1 to an exercise or a no exercise control group (four groups). The supervised exercise intervention comprises 3 weekly HIIT sessions on an ergometer bicycle. The primary outcome is the change in left ventricular mass (LVM), and key secondary outcome is change in visceral fat mass. Both outcomes are measured by MRI. Primary statistical analysis will evaluate LVM at follow-up in a regression model. Intention-to-treat and per protocol analyses will be conducted. The latter necessitates a minimum attendance

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Supervised intervention (high-intensity interval training) is individually tailored with progressive load increments based on aerobic capacity and maximal heart rate, which produces optimal conditions for cardiovascular adaptions.

⇒ Repeated MRI before and after intervention, provides a robust basis for detecting cardiac and metabolic adaptions to exercise, in rheumatoid arthritis (RA) patients in stable tumour necrosis factor (TNF) inhibitor or interleukin 6 (IL-6) signalling inhibitor treatment.

⇒ Blinding of patients to intervention (exercise training) and investigators to biological disease-modifying antirheumatic drugs (bDMARDs) treatment during the study is not possible.

⇒ The cardiac and metabolic effects of exercise in RA patient in stable treatment with TNF inhibitor or IL-6 inhibitor is limited to the length of the study (12 weeks).

⇒ Recruited RA patients are stratified for bDMARDS prior to randomisation. This stratification may induce inherent differences between otherwise comparable groups.

rate of 80%, adherence to bDMARDs treatment of ≥80% and minimum 8 min (50%) of maximal heart rate above 85% per session.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by synovial inflammation and hyperplasia, bone and cartilage destruction, systemic inflammation and production of disease-specific autoantibodies.[1] While the pathogenesis of RA involves a complex interplay between genetic factors and external factors that remains to be fully elucidated, systemic inflammation is a central component shown to mediate a 1.5–2-fold increased cardiovascular disease (CVD) risk in patients with RA, independent of conventional risk factors.[2–4]

In RA, a dysregulated immune response, causes B-lymphocyte and T-lymphocyte to overexpress several pro-inflammatory proteins, including tumour necrosis factor (TNF) and interleukin 6 (IL-6).[5 6] This chronic inflammatory state is not limited to the joints. Sustained elevated levels of TNF and IL-6 affect tissues in various ways. TNF contributes to the metabolic syndrome by inhibiting insulin signalling and accelerating atherosclerosis.[7–9] In a chronic setting, TNF also mediates the secretion of IL-6.[10] Here, IL-6 is associated with development of type 2 diabetes[11] and myocardial infarction and stroke.[12] These findings provide a mechanistic basis for the increase in CVD events associated with RA in clinical studies.[4 13]

IL-6 is not only a pro-inflammatory cytokine, it is also a myokine released from exercising skeletal muscle in response to muscle contraction.[14] Thus, following exercise, plasma levels of IL-6 are acutely upregulated manyfold. Importantly, there is no equivalent increase of TNF.[15] In contrast to the chronic inflammatory state, exercise-induced IL-6 is TNF-independent and may in fact attenuate the plasma levels of TNF.[16] We recently showed that the myokine IL-6 is required for the exercise-associated loss of visceral fat mass in abdominally obese humans following 3 months of exercise training.[17 18] The study also showed that IL-6 is necessary for the physiological increase in left ventricular mass (LVM) seen after a period of exercise training, but the explanation of these seemingly physiological effects of IL-6 remain to be elucidated in detail.

Scientific studies have evidenced that high-intensity interval training (HIIT) is a potent approach to improve cardiovascular fitness. HIIT is superior in terms of time efficiency compared with moderate intensity training, with intervals that last at least 2 min being the most efficacious in enhancing cardiovascular fitness.[19] The European Alliance of Associations for Rheumatology (EULAR) guidelines suggest incorporating physical activity into daily routines for individuals with RA, and there is no clear evidence indicating that high-impact exercise should be avoided during active RA.[20 21] The physiological alteration of LVM due to high-intensity exercise is a known phenomenon, and it is known to occur before other cardiac adaptations.[22–24] MRI is a highly effective tool for detecting changes in LVM.[25] Although an increase in LVM in response to a pathological condition, particularly hypertension, is linked to higher cardiac morbidity and mortality, the physiological change in LVM caused by exercise is associated with a maintained mass-to-volume ratio, improved left ventricular function, reduced mitochondrial dysfunction and preserved diastolic function.[26–28]

Despite the involvement of IL-6 signalling in the cardiometabolic adaptations to exercise, it is still unknown[29] whether this translates into blunted exercise adaptations in patients with RA treated with IL-6 signalling inhibitors (IL-6i). The EULAR recommendations[30] do not differentiate between specific biological disease-modifying antirheumatic drugs (bDMARDs) in combination with a conventional synthetic disease-modifying antirheumatic drugs. Presently, IL-6i and TNF inhibitors (TNFi) are considered equal in terms of effect and safety for the management of RA patients. Based on market prices, TNFi have in Denmark traditionally been prioritised for first line bDMARDs treatment of RA. However, the percentage of patients with RA treated with TNFi, as first line treatment, has significantly declined over the last decade. This is due to the introduction of new therapeutic targets and drugs with other modes of action including IL-6i.[31] Thus, it is of clinical value to compare how patients with RA treated with IL-6i and TNFi adapt to an exercise training intervention. At present, randomised clinical trials that investigate the cardiometabolic adaptations to exercise in patients with RA treated with stable IL-6i or TNFi are lacking, and we anticipate that this study will offer novel perspectives on the significance between bDMARDs and the adaptation to exercise in patients with RA.

Study objectives and hypotheses

The primary objective is to investigate whether cardiac adaptations to exercise training, measured by change in LVM, differ between patients in stable treatment with IL-6i and TNFi. The secondary objective is to investigate whether metabolic adaptions to exercise training, notably changes in visceral fat, differ between patients with RA in stable treatment with IL-6i and TNFi.

We hypothesise that pharmacological inhibition of IL-6, but not pharmacological inhibition of TNF, impairs exercise-induced changes in cardiac ventricular mass. Furthermore, we hypothesise that pharmacological inhibition of IL-6, but not pharmacological inhibition of TNF, reduces exercise-induced loss of visceral fat mass.

METHODS

Study design

The study is an open label, controlled, investigator-blinded, randomised study. Patients with RA (n=80) in
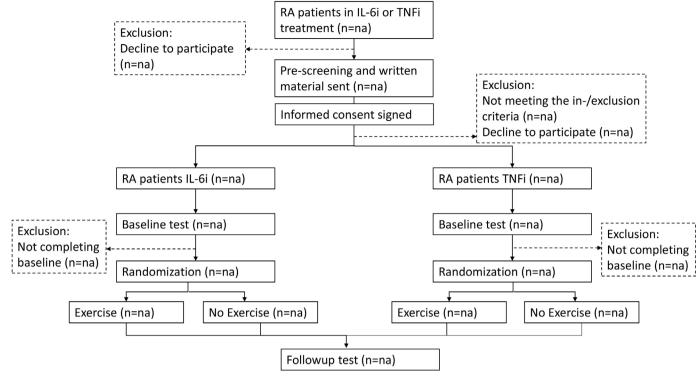
Figure 1 Flowchart of study. IL-6i, interleukin 6 signalling inhibitors; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitors.

stable bDMARDs treatment undergo 3 weekly supervised exercise sessions or no exercise (control groups) for 12 weeks. Enrolled patients are stratified for bDMARDs treatment (IL-6i or TNFi) and sex prior to a 1:1 block randomisation in blocks of 10 resulting in four groups (n=20), figure 1. No new drugs or changes in medical treatment are introduced due to this study, and supervised exercise is the single intervention.

The enrolment period commenced in December 2021 and is planned to run until 31 December 2023 or when 80 patients have been included, or the end criteria (described further below) are met. Follow-up and data collection are estimated to be completed by the spring of 2024. Baseline and follow-up tests are carried out at Centre for Physical Activity Research (CFAS) Rigshospitalet and the Department of Cardiology Rigshospitalet, Denmark. All data are collected and analysed in Denmark. Patients are randomised immediately following successful baseline completion. The follow-up visit will be identical to the baseline visit.

Recruitment

Patients are recruited in collaboration with rheumatologists at RA outpatient clinics throughout Zealand, Denmark. Recruitment will follow one of two methods:

1. Patients are invited to participate in the study by a physician or nurse at their local outpatient clinic. Patients are provided contact information to the physician and study investigator.
2. Outpatient clinics provide a list of potential eligible patients, and the study investigator reach out to the

patients by email through a secure digital platform. Patients interested in participation are urged to contact the study investigator by e-mail and a telephone call between patient and the study investigator is planned.

Eligibility

Inclusion and exclusion criteria are detailed in table 1. A low DAS-28-ESR[32 33] score of ≤3.2 was chosen, as it is expected, that including patients with low and stable disease activity in the study will improve uniformity and accuracy of measuring the relationship between bDMARDs and exercise outcomes, while minimising the impact of inflammation. Substituting therapy or steroids for patients with high disease activity during the study could introduce bias. Patients with high DAS-28-ESR scores at baseline are likely to improve regardless of exercise due to intensified therapy and regression towards the mean. Patients with less severe symptoms are expected to have better adherence to the intervention.

Patients may be deemed ineligible for participation in the study if they have certain health conditions, such as cognitive disorders (dementia) psychiatric conditions (schizophrenia), physical limitations that prevent them from performing the intervention (such as being confined to a wheelchair), or current or past CVDs that are determined to be exclusionary on a case-by-case basis in accordance with existing guidelines.[34] If any concerns arise about the safety of a patient, a cardiologist designated by the study is consulted.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

► Age ≥18 and <70 years
► Informed consent
► Diagnosed RA based on the 2010 American College of Rheumatology/EULAR criteria[57]
► In treatment with bDMARD either IL-6i og TNFi >4 months prior to enrolment
► Low RA disease activity, based on the DAS-28-ESR for RA ≤3.2
► An ECG without features of left ventricular hypertrophy defined by the European Society of Cardiology[58]
► Females of childbearing potential have to use one or more of the following highly effective methods for contraception in order to be included:
  – Vasectomised partner
  – Bilateral tubal occlusion
  – Sexual abstinence
  – Intrauterine device
  – Hormonal contraception
► Females who are considered to have no childbearing potential are
  – Bilateral tubal ligation
  – Bilateral oophorectomy
  – Complete hysterectomy
  – Postmenopausal defined as 12 months with no menses without an alternative medical cause
	► Health conditions that prevent participating in the exercise intervention
	► Subjects who cannot undergo MRI scans (metallic implants or claustrophobia)
	► Corticosteroid use per os >10 mg/day within 7 days of study enrolment
	► Intramuscular corticosteroid within 3 weeks of the study enrolment
	► Grade 2 hypertension (systolic BP >160 mm Hg and/or diastolic BP >100 mm Hg)[58] despite the use of antihypertensive drugs
	► Pregnancy
	► Subjects with insulin dependent diabetes

BP, blood pressure; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; IL-6i, interleukin 6 inhibitors; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitors.

Medical treatment

As this study does not seek to assess one specific drug the Danish Medicines Agency has accepted that the authors select one drug in each category of TNFi (AMGEVITA, Amgen) and IL-6i (Kevzara, Sanofi) as representatives in the product resumes.[35 36] Patients enrolled may be treated with any kind of either TNFi or IL-6i. There will be no changes to the handling and storage of bDMARDs due to this study.

Exercise intervention

The exercise programme consists of HIIT on ergometer bicycles. The training consists of 10 min of warm up at 40%–60% maximum heart rate (HR_{max}), followed by 25 min of HIIT (4 bouts of 4 min at >85% HR_{max} interspaced by 3 min of low intensity at 40%–60% HR_{max}) and finally a 5 min cool-down of 50% HR_{max}. The maximal oxygen consumption rate (VO_{2max}) will be performed at baseline and will determine relative workload accordingly.

All sessions will be supervised and administered by experienced trainers. To ensure proper intensity, all patients will wear a heart rate monitor and adequate changes to the load are performed if necessary. Each training session will be documented (attendance, total time of HR_{max} >85%, total time of exercise, average wattage, average heart rate and perceived exertion (Borg scale[37])).

Assessments

On written and oral information by a physician and once the informed consent form has been signed, patients are invited to the baseline visit. The assessments at baseline and follow-up are described in details below and include a general medical health examination, a whole-body dual X-ray absorptiometry (DXA) scan, blood samples, an oral glucose tolerance test (OGTT), a transthoracic echocardiography (TTE), a pulmonary function test (diffusing capacity, dynamic spirometry, body plethysmography), a VO_{2max} test, a cardiac and abdominal MRI scan, and the following questionnaires: The Short Form (SF-36) Health Survey[38] and The Health Assessment Questionnaire Disability Index (HAQ-DI).[39] Half-way (week 6), a 3-day dietary record is obtained. Patients will wear axial accelerometer-based physical activity monitors (AX3) at the follow-up visit for five consecutive days to measure activity level, figure 2.

Medical assessment

At baseline and follow-up each patient undergoes a medical examination by an experienced physician not blinded to the medical treatment but blinded to intervention. The assessment includes auscultation of heart and lungs, a brief medical history (only baseline), general physical activity level, ECG, blood pressure, all current
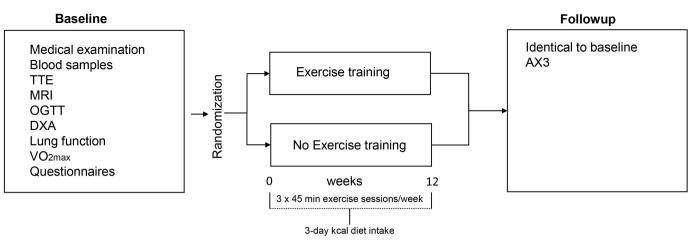
Baseline

- Medical examination
- Blood samples
- TTE
- MRI
- OGTT
- DXA
- Lung function
- VO$_{2max}$
- Questionnaires

Randomization

Exercise training

No Exercise training

Followup

Identical to baseline
AX3

0   weeks   12

3 x 45 min exercise sessions/week

3-day kcal diet intake

Figure 2 Overview of study and tests. AX3, axial accelerometer-based physical activity monitors; DXA, dual-energy X-ray absorptiometry; LVEF, left ventricular ejection fraction; OGTT, oral glucose tolerance test; TTE, transthoracic echocardiography; VO$_{2max}$, maximal oxygen consumption.

drug use, the start and end date of all drug use related to the treatment of RA since the time of diagnosis (only baseline), and a joint count test to assess tender and swollen joints. Data related to the medical assessment, not including auscultations and ECG will be reported.

Maximal aerobic capacity

To determine the VO$_{2max}$ patients perform a standard graded exercise test on a bicycle ergometer (Monark LC4, Monark Exercise AB, Vansbro, Sweden) at CFAS. Following a 5 min warmup at 50 W, the workload is increased by 20 W every minute until exhaustion. Exhaustion is categorised as either voluntarily or a cadence below 60. An appropriate test quality is confirmed if the respiratory exchange ratio is >1.1, and oxygen uptake plateaus despite increasing workload. Minute ventilation and expired CO$_2$ and O$_2$ will be measured by indirect calorimetric measurements (Quark b2, Cosmed, Rome, Italy). HR$_{max}$ is determined as the peak heart rate during the final minute of the VO$_{2max}$ test[40] at baseline.

Cardiac and abdominal MRI

The cardiac MRI takes place at Rigshospitalet, Denmark, using a 1.5 T whole body scanner. Steady-state free precession cine images are obtained during repeated breath holds in three long axes and in a stack of short axes covering the entire heart to rule out wall motion abnormalities and allow for cardiac chamber and mass quantification. Tissue characterisation with parametric mapping will be performed. Gradient echo phase-contrast cine MRI with ECG gating are used to evaluate aortic and pulmonary artery flows and areas. Images of the ascending and descending aorta are acquired in the transverse plane perpendicular to the aortic lumen at the level of the right pulmonary artery. Images of the pulmonary arteries are acquired in two planes perpendicular to the main pulmonary artery and left pulmonary artery, respectively. Semi-automatic evaluation using commercially available software (cvi42, Circle Cardiovascular Imaging, Calgary, Canada) are applied for postprocessing. If necessary, the

automatic contour detection of the left ventricular endocardium and epicardium is corrected manually according to guidelines.[41] On this basis, parameters including myocardial mass, left ventricular ejection fraction, stroke volume, end-diastolic volume, end-systolic volume and strain measures will be derived. Abdominal and cardiac fat is imaged by a volumetric interpolated breath-hold examination using two-point Dixon fat-water separation covering the entire abdomen in the axial plane and in a subset of long and short axis cardiac planes. Evaluation is conducted with semi-automatic calculations, with manual correction, if necessary, using commercially available image analysis software (Slice-O-matic; Tomovision, Montreal, Quebec, Canada). Liver fat content is evaluated by spectroscopy within a 27 cm^3 voxel in the mid right liver lobe avoiding of large vessel. Finally, intramyocardial triglyceride content are quantified within a ~4 cm^3 voxel placed in the interventricular septum using a spin-echo excitation scheme with both of ECG and respiratory triggering added to the spectroscopy sequence. Postprocessing is conducted using on-scanner software (syngo.via, Siemens Healthineers, Erlangen, Germany). All MRI scans are analysed in a blinded manner.

Transthoracic echocardiography

TTE is performed at CFAS to assess changes in cardiac function and structure. The images are acquired and analysed with GE Vivid E95 (GE Vingmed Ultrasound, Horten, Norway) and GE Echopac software. Patients are examined in the left lateral decubitus position. All echocardiograms are obtained by a trained physician and analysed and validated by a cardiologist who is blinded to the allocated study group. The acquisition of images is done according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[42] In parasternal long axis view, the left ventricular wall thickness is determined at end-diastole at the level of the mitral valve leaflet tips. Ventricular mass will be calculated by the formula: 0.8×1.04×[(interventricular

septum+LV internal diameter+posterior wall thickness)^3–(LV internal diameter)^3]+0.6 g. LV ejection fraction is determined by Simpson's biplane method. Left atrial volume is determined by the biplane area-length method. The early (E) to late (A) ventricular filling velocity ratio (E/A), is determined by Pulsed-wave doppler in apical four-chamber view. The early mitral annular diastolic velocity (e′) is determined in both the septal and lateral region using the four-chamber view. Global longitudinal strain is determined with speckle tracking in the two-chamber, three-chamber and four-chamber apical view using a semi-automated function to trace the myocardium throughout the cycle according to practical guidelines.[43] If necessary, the automatic tracing is corrected manually.

Body composition

To analyse fat mass and lean body mass, patients undergo a DXA (Lunar Prodigy GE Heathcare, Madison, Wisconsin, USA. enCORE software V.14, 10, 022), under the supervision of experienced staff.

Activity record

Posture allocation and physical activity behaviours are measured using axial accelerometer-based physical activity monitors (Axivity AX3, Newcastle, UK). Patients are equipped with two accelerometers for five consecutive days at the follow-up visit. One is placed on the right thigh, and one is placed on the right side of the lumbar.[44] Both accelerometers are attached on the subject with a patch (Fixomull stretch, BSN medical, Germany). The patients are asked to document the time of day they wake up and go to bed, working and exercising hours.

Diet record

The patients are encouraged not to change their dietary intake during the study. A self-reported 3-day record of total dietary intake is obtained half-way through the intervention period.

Lung function

Standardised lung function testing is performed in accordance with consensus guidelines at using equipment at CFAS. This encompasses dynamic spirometry,[45] body plethysmography[46] and diffusing capacity.[47] Based on summary equations,[48 49] the expected values according to height, age and sex will be calculated.

Blood samples

Fasting (minimum of 10 hours) blood samples are drawn in the morning at CFAS. Blood samples are drawn throughout the OGTT. Samples will be analysed according to standard procedure at the Department of Clinical Biochemistry, Rigshospitalet. On centrifugation, all plasma will be transferred to Eppendorph tubes and stored at −80°C. Plasma will be analysed for IL-1Ra, IL-1β, IL-6, IL-10, IL-15, TNF, high-sensitivity troponin and high-sensitivity C reactive protein.

Oral glucose tolerance test

A standard 2-hour 75 g OGTT is performed with a serial of blood samples drawn at baseline, and after 15, 30, 60, 90 and 120 min.[50 51]

RA disease activity measures

RA disease activity is assessed by HAQ-DI and quality of life by SF-36. HAQ-DI is a tool to asses functionality of RA. It is a self-reported questionnaire in Danish[52] that covers eight sections, each with 2–3 statements with a total number of 20, along with 14 items regarding assistance devices. SF-36 is a 36-item self-reported health survey in danish[53] that covers eight health concepts, including social functioning, fatigue and general well-being.

Outcomes

The primary outcome is the change in LVM (g) measured by MRI. The key secondary outcome is visceral fat mass, measured by MRI. We consider all further secondary outcomes to be of exploratory nature and supportive of the primary outcome. A full list of outcomes is depicted in table 2.

Criteria for discontinuation and withdrawal

If the patient experiences severe side effects related to the exercise training, or it is deemed unsafe for the patient to continue exercise training, by an unblinded medical doctor, the patient will be withdrawn from the exercise training intervention but encouraged to participate in the follow-up visits. A patient may choose to withdraw from the study at any time.

Concomitant care and compliance

Concomitant long-term medication should preferably be taken at a stable dose at least 1 month prior to enrolment and remain stable throughout the study period. All drugs taken prior to and during the study will be documented. Patients are urged to inform the study staff about over-the-counter pain treatment or an increased use in already prescribed pain treatment or newly prescribed medication during the study. To maintain the benefits of randomisation, the patients will be offered to attend follow-up visits despite protocol violations or discontinuation. To take part in the per protocol analysis, the patient must have attended no less than 29 of 36 sessions (80%). Each exercise session will be considered completed if the patient reaches ≥85% of HR_{max} for no less than 8 min (50%) during the intervals (4×4 min). Patients will be offered additional sessions to reach the target.

To be included in the per protocol analysis, the compliance to the background bDMARDs treatment must be 80% or higher. If a patient forgets/misses a dose, he/she must follow the local outpatient guidelines. All new medication initiated during the study period will be documented during compliance telephone calls at week 4, 8 and at follow-up.

Table 2 Outcomes

Primary outcome	Measurement
Left ventricular mass (g)	MRI
Key secondary outcome	
Visceral fat mass (g)	MRI
Secondary outcomes	
Stroke volume (mL)	MRI and TTE
End diastolic volume (mL)	MRI and TTE
Left ventricular ejection fraction (%)	MRI and TTE
Global longitudinal strain (%)	MRI and TTE
Early to late ventricular filling ratio (E/A ratio)	MRI and TTE
Early ventricular filling to early diastolic mitral annular tissue velocity (E/é.ratio)	MRI and TTE
Left ventricular and atrial end-systolic volume (mL)	MRI and TTE
Left atrial volume index (mL/m^2)	MRI and TTE
Interventricular septum thickness (mm)	MRI and TTE
Left ventricular posterior wall thickness (mm)	MRI and TTE
Functional vascular parameters: aortic and pulmonary distensibility (10^{-3}mmbHg^{-1}) and pulse wave velocity (m/s)	MRI
Adipose tissue: subcutaneous, visceral and epicardial (g)	MRI
Intramyocardial triglyceride content and liver fat content (%)	MR spectroscopy
Cardiorespiratory fitness (mL/kg/min)	VO$_{2max}$ test on Monarch LC4 with CosMed system
Dynamic spirometry (FEV$_1$/FVC)	Lung function equipment
Body plethysmography (TLC)	Lung function equipment
Diffusion capacity (mL/min/mm Hg)	Lung function equipment
Body composition	DXA and MRI
Oral glucose tolerance test	p-glucose (mmol/L), p-insulin (pmol/L), proinsulin C-peptide (nmol/L)
Axial accelerometer-based physical activity monitors	5-day measurement by AX3
Dietary report	3-day self-reported measurements
Blood samples	Total cholesterol, LDL-cholesterol and HDL-cholesterol, triglycerides (mmol/L), SR (sedimentation rate) (mm/hour), CRP (mg/L)
Tender and swollen joints	66/68 tender and swollen joint count
Joint pain, Patient Global Assessments, Physician Global Assessment (0–10 cm)	VAS
Physical disability (0–3)	HAQ-DI
Health related quality of life	SF-36
Disease activity DAS-28-ESR	DAS28 (ESR)
CDAI-response	CDAI minor/moderate/major response[59]
ACR-response	ACR 20/50/70 response[60]
Eular response	EULAR none/good/moderate response[61]

ACR, American College of Rheumatolgy; AX3, axial accelerometer-based physical activity monitors; BMI, body mass index; CDAI, Clinical Disease Actitivity Index; CRP, C reactive protein; DAS28, Disease Activity Score-28; DXA, dual-energy X-ray absorptiometry; E/A, early to late diastolic transmitral flow velocity ratio; EDV, end-diastolic volume; E/e, early mitral inflow velocity and mitral annular early diastolic velocity ratio; ESR, erythrocyte sedimentation rate; ESV, end-systolic volume; EULAR, European Alliance of Associations for Rheumatology; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; GLS, global longitudinal strain; HAQ-DI, Health Assessment Questionnaire Disability Index; HDL, high-density lipoprotein; IVS, interventricular septum; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; OGTT, oral glucose tolerance test; PW, posterior wall; SF-36, Short Form 36 Health Survey; SV, stroke volume; TLC, total lung capacity; TTE, transthoracic echocardiography; VAS, visual analogue scale; VO$_{2max}$, maximal oxygen consumption.

Randomisation and allocation concealment

The randomisation code will be placed on a secure password protected server. An employee of CFAS who is not otherwise involved in any related procedures regarding this study will randomise the patient through an automatic randomiser using Microsoft Excel. The employee will provide information regarding group allocation to an unblinded researcher affiliated with this study, that will inform the patient. Allocation concealment will be implemented using a web-based trial management system (EasyTrial). Outcome assessors are blinded to allocation at follow-up. Due to the nature of the study, blinding of intervention to patients is not possible.

End criteria

Inclusion period will end 26 months after the first subject has been recruited or if at least 16 patients in each group have been deemed fully compliant or further inclusion rate is below to patients per month.

Confidentiality

Confidentiality of the patients will be maintained by assigning a study number, keeping identifiers separate from the data and storing data in a locked file in a secure computer database. Scientific reports generated from the study will be anonymised. Data will be managed through EasyTrial and data entry is performed immediately following study visits by an unblinded assessor.

Power and sample size considerations

The power analysis on the change in LVM is based on similar studies.[18 54] To detect a change of 12 g (SD 12.3) between exercise groups (TNFi vs IL-6i) assuming a 5% alpha-level in a two-sided unpaired t-test with homoscedasticity and a power of 80% (1−β), a sample size of 16 in each group is needed. To account for potential dropouts, we will include 20 patients in each group (n=80). No previous studies have determined the effect of TNF on cardiac adaptations following exercise, thereby limiting our power analysis to either placebo or IL-6i.

General analysis plan

Statistical analysis of data will be performed in R (latest version). Data will be presented in an explanatory and a pragmatic approach.[55] Therefore, the primary outcome will be assessed by intention-to-treat and per protocol analysis. Descriptive analysis of patient characteristics will be performed before and after the intervention and will be expressed as means±1 SD, or if not normally distributed as means and IQRs.

The primary statistical analysis will be a multiple regression model to account for the primary outcome at follow-up (LVM_{FU}) by the following covariates: primary outcome at baseline (LVM_{BL}), sex, bDMARD group, intervention group; as the primary analysis we will also look for an interaction between bDMARD group and intervention group; if this is non-significant the interaction will be deleted from the final model.

Key secondary outcome will be handled in a similar fashion. Secondary outcome and exploratory outcomes will be handled as follows; quantitative outcomes will be analysed using a linear regression model with the follow-up value as the outcome and the baseline value as a covariate, stratifying for sex, bDMARDs and intervention as above (including interaction between bDMARDs and intervention). Categorical outcomes will be handled similarly using a multinomial logistic regression model, count data will be handled with Poisson regression (online supplemental table S1). A full statistical analysis plan will be made public prior to unblinding.

No interim analysis will be performed. Multiple attempts will be made to obtain missing data. All reported p values will be two-sided. The statistical significance is set at the conventional level of 0.05 (p<0.05). Outcomes will not be analysed before the study is finalised. Results will be reported in accordance with the Consolidated Standards of Reporting Trials.[56]

Patient and public involvement statement

Patients or the public were not involved in the design of the study. We include patient reported outcome measures and patients are urged to provide feedback about the burden of the intervention, thereby providing important information regarding feasibility throughout the study.

ETHICS AND DISSEMINATION
Safety

During the study, approximately a total of 100 mL blood will be drawn on two separate days, with a minimum of 12 weeks apart, by an experienced laboratory staff. The risks of dizziness, infections or anaemia are considered minimal. VO_{2max} and lung function testing are considered safe but may cause patients to feel dizzy immediately following the test. A TTE following standard clinical procedures is considered safe. A DXA scan will provide an effective radiation dose in the range of 3–30 µSv—equivalent of 3 days of background radiation in Denmark and is considered safe. An MRI scan contains no iodising radiation and is considered safe. However, some patients may experience discomfort while lying still within a constrained space during the scan. The MRI procedure will be thoroughly explained to the patient prior to the scan, and trained staff will be present. Patient safety is prioritised through telephone calls at week 4 and 8 during the intervention. Any potential safety issues are addressed during these contacts, and an unblinded affiliated physician is available for consultation if necessary. All adverse events will be documented. All serious adverse events (death, life-threatening, requires hospitalisation >24 hours or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity expected or unexpected) will be documented and reported to the Danish medicines Agency and the Capital Region Ethics Committee. Audits and Data monitoring

by is performed by the GCP-unit of Copenhagen, which is independent from the study sponsor.

Trial investigators will have full access to the data set, and there are no other contractual agreements that limit such access. The results of the study, both positive, negative and inconclusive, will be disseminated through a systematic dissemination and publication strategy, as well as uploaded to clinicaltrialregister.eu as soon as possible, and at the latest, 1 year after end of study. After this, the manuscript will then be submitted to peer reviewed scientific journals.

The study has been approved by the Regional Ethics Committee (H-21010559 with amendments 86424, 87463 and 88044) and the Danish Medicines Agency (2021-005287-21) prior to recruitment. All study outcomes will be collected after written signed consent (online supplemental file 2). No changes to the protocol will take place without prior acceptance from the Danish Medicines Agency and/or the Regional Ethics Committee.

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Contributors RHC, BKP, PH, HE and RMGB conceived the study. SJønck, RHC, RMBG, MLA, PH, HE and SJacobsen initially designed and planned the study. RHC, SJønck and MLA elaborated on the statistical design of the study. MAVL and NV elaborated on the MRI scan design. SJønck wrote the first manuscript draft. MLA, PH, IER, HE, MAVL, PGJ, SJacobsen, LK, NV, LD, BKP, RMGB and RHC made critical revisions and approved the final manuscript.

Competing interests PGJ has received lecture fees from Astra Zeneca and Novo Nordisk. MLA has received speaking fees from Novartis. LK has received lecture fees from Novo, Novartis, AstraZeneca, Bayer and Boehringer. LD has received speaking fees from Eli Lilly, Galderma and Janssen and research grant from BMS outside the present work. RHC is currently employed at Novo Nordisk, Denmark. All other authors declare no conflicts of interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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

Provenance and peer review Not commissioned; externally peer reviewed.

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