

Supplement 1. Original Protocol

Introduction

Cardiac rehabilitation (CR) is a well established health service for the secondary prevention of heart disease, particularly following an acute event and/or hospitalization. Exercise training forms an integral part of lifestyle modification to improve health outcomes, and moderate intensity continuous training (MICT) has been the cornerstone of exercise prescription for CR. There is substantial evidence from several meta-analyses [1-4] that CR services involving exercise can significantly reduce cardiovascular disease and all-cause mortality by 20-35% and 20-40% respectively. Exercise capacity, measured directly as peak oxygen uptake (peak VO_2), has been shown to exert the largest influence on cardiovascular disease prognosis in this population [5]. High intensity interval training (HIIT), which involves alternating periods of high intensity exercise with light recovery exercise, has been shown to elicit greater improvements in peak VO_2 than moderate intensity continuous training (MICT) in people with coronary artery disease (CAD) [6-11] and remarkably in those with heart failure [12]. While HIIT is now recognized internationally in CR exercise guidelines as an appropriate and efficient modality for improving cardiovascular health in patients with CAD [13], a recent survey of CR centres by our team found safety concerns to be the leading barrier for implementing HIIT as standard care [14]. Although it has been demonstrated that higher exercise intensities elicit greater cardioprotective effects than MICT [15], there are still concerns that high intensity exercise may increase the risk of sudden cardiac death and myocardial infarction in susceptible persons [16].

The interest in use of HIIT for CR has resulted in large randomized controlled trials, such as the Saintex CAD study (n=200) [17], the Smartex HF study (n=220) [18] and studies by Aamot and colleagues (n=83) [19], and Moholdt et al (n=59) [20]. These studies showed variable results, likely due to differing levels of adherence to prescribed exercise intensities of the HIIT and MICT protocols. To date, most studies utilize objective measures of exercise intensity (such as heart rate (HR)) rather than subjective measures (such as rating of perceived exertion (RPE)). RPE is more commonly used in Australian CR as few patients undertake a maximal exercise test to determine their true maximal HR [21]. Additionally, using a % of a measured 'maximal' HR may not be an accurate measure of intensity if maximal HR is not achieved during the graded exercise test, or beta blockade dose/timing is different between testing and training. Major limitations reported by the Saintex CAD study [17] was the lower average training HR of HIIT ($88\%HR_{\text{peak}}$) and higher average training HR of MICT ($80\%HR_{\text{peak}}$). Although training intensity was not determined by RPE in this study, the average reported RPE was 13.5 for HIIT and 12.5 for MICT. Additionally, while the Smartex HF study reported an average training HR of $90\%HR_{\text{peak}}$ for HIIT, 51% of HIIT participants were training below their target HR. Both the Saintex CAD study [17] and Smartex HF study [18] highlighted the necessity in clinical practice to adjust objectively defined HR targets and workloads according to a patient's subjective feelings. Another limitation of the current literature is many studies also use only one exercise modality [17, 20, 22], which is not reflective of a real world setting where various exercise modalities are used.

Visceral adipose tissue (VAT) is also considered an important contributor to a lifetime risk of cardiovascular morbidity and mortality (cardiometabolic risk), in conjunction with traditional cardiovascular risk factors [23]. We have recently shown that exercise training can reduce both VAT and intra-hepatic lipid [24], and interval training protocols, of varying nature, have shown significant reductions in VAT of up to 48% in 8 weeks [25-28]. To our knowledge, no studies have investigated the effect of HIIT versus MICT on VAT in people with CAD.

The current study has been designed to assess feasibility, safety, adherence, and efficacy of HIIT compared with MICT, in a real-world CR setting. Specifically, it will assess whether HIIT is superior to MICT when subjective measures of exercise intensity (RPE) and various exercise modalities are utilized.

The primary aim of this study is to determine the effect of HIIT compared with MICT on cardiorespiratory fitness (VO_{2peak}) in patients with CAD undertaking a 4-week cardiac rehabilitation program.

The secondary aims of this trial are to investigate:

- If HIIT is equally feasible and safe, compared to MICT
- The effect of HIIT compared with MICT on cardiorespiratory fitness (VO_{2peak}) in patients with CAD following 3 months, 6 months, and 12 months of exercise training.
- The effect of HIIT compared with MICT in patients with CAD on exercise adherence, body composition, vascular function, inflammatory markers, intrahepatic lipid, energy intake, and dietary behavior following 4 weeks, 3 months, 6 months, and 12 months of exercise training.
- The effect of HIIT compared with MICT in patients with CAD on VAT following 3 months of exercise training.
- The effectiveness of HIIT and MICT coupled with technology (wrist worn monitors) on exercise adherence during an 8-week home-based program following a 4-week supervised cardiac rehabilitation program.

The feasibility and safety of prescribing HIIT within a real world environment is important as group settings can involve patients with varying levels of disease, functional limitation, and ability to exercise independently. We hypothesize that HIIT will be equally feasible and safe for a CAD population and HIIT will achieve superior outcomes for peak VO_2 , VAT, and other cardiometabolic parameters. Additionally, we hypothesize the use of technology will improve exercise adherence during home-based training.

Methodology

Ethics and trial registration

The study protocol has been granted approval by UnitingCare Health Human Research Ethics Committee (#1522) and The University of Queensland Institutional Human Research Ethics Committee (#2015001938). The study adheres to the Helsinki Declaration and is prospectively registered with Australian New Zealand Clinical Trial Registry (anzctr.org.au) identifier: ACTRN12615001292561p (26 November 2015).

Study design and setting

The FITR Heart Study is a single centre prospective randomized controlled trial conducted within a tertiary hospital, which will facilitate voluntary participant recruitment and the supervised CR program component. All CR staff will receive training on how to integrate the intervention training into the current CR class timetable. All other aspects of the CR program will be unaffected. As this study runs parallel to clinical practice, all medical management, including medication prescription, will be at the discretion of the treating physician. Therefore, these factors cannot be controlled but all changes will be documented and considered during analysis.

The study will consist of three stages (Table 1).

Stage	Timeframe	Weekly Exercise Training	Level of support
Stage 1	4 weeks	2 supervised sessions per week + 1 home-based session per week	Supervised exercise classes
Stage 2	8 weeks	Minimum of 3 home-based sessions per week	Weekly support
Stage 3	9 months	Minimum of 3 home-based sessions per week	None

Table 1: Outline of study stages

Stage 1 will involve a 4-week supervised CR program, consisting of 2 supervised sessions and 1 home-based session per week. Four weeks was chosen as the current practice in this facility is 8-10 supervised exercise sessions throughout the cardiac rehabilitation program. Participants will receive education on how to monitor and progress their exercise training appropriately. RPE will be the primary method for prescribing exercise intensity for both groups.

Stage 2 will involve an eight-week home-based program with weekly support, consisting of at least 3 home-based sessions per week of their randomized training. Participants will be asked to submit exercise training records via email on a weekly basis and will be provided with support and motivation if they do not adhere with the exercise protocol. During this stage, participants will be further randomized to FIT-TRACK or non-FIT-TRACK groups for the duration of Stage 2. FIT-TRACK participants will be provided with a wrist worn **FITness TRACKing** HR monitor (Fitbit Charge HR™, Fitbit Inc., San Francisco, United States), and instructions for use and integration with their smart phone or computer. Participants are instructed to use the device as they desire to monitor and track their exercise program and overall physical activity levels. Data will be

automatically extracted from the Fitbit Application Programming Interface (API) using software developed by our team. The goal of FIT-TRACK is to use technology to increase exercise adherence following a CR program.

Stage 3 will involve maintenance of the Stage 2 program, whereby participants will be encouraged to continue their home-based exercise program but without weekly support.

Participants and eligibility criteria

To be deemed eligible for the study, participants must have angiographically-proven CAD (determined by the treating physician) and be aged between 18-80 years old. Participants may have a history of: acute coronary syndrome, coronary artery bypass graft surgery, or valvular surgery (> 4 weeks); percutaneous coronary intervention (> 3 weeks); or stable heart failure. Patients will be excluded from participation if they have any absolute or relative contraindications to exercise testing as per the American Heart Association guidelines [29], including but not limited to: unstable angina; unstable arrhythmias, severe valvular disease; uncompensated heart failure; severe pulmonary disease; uncontrolled hypertension (systolic blood pressure > 200 mmHg and/or diastolic blood pressure >110 mmHg); chronic kidney disease (stages III-V); orthopedic/neurological limitations; or physical impairment limiting the ability to exercise. Additionally patients will be excluded for: indicating an unwillingness to comply with one of the exercise prescriptions they may be randomized to; planned operations during the research period; drug or alcohol abuse; planning to, or participation in another intervention study; not willing to sign the consent form; and pregnancy or expecting to be pregnant during the study period.

Recruitment

The study aims to recruit 100 men or women with diagnosed CAD. During phase one of CR patients are referred to a phase two CR program following a hospital admission for a cardiac related event or procedure. Specialized cardiac nurses visit patients on the hospital ward during recovery to discuss CR and organize an initial CR assessment interview if appropriate. This initial CR assessment interview is where patients eligible to participate in the phase two CR program, and who meet study criteria, will be given the opportunity to participate in this study. Study information brochures will be provided to participants in hospital or at their initial CR appointment. If the patient expresses interest in study participation, a further screening process will be completed by the chief investigator, and the study requirements will be explained to the patient in detail verbally and via the written Patient Information and Consent Form. Once a patient confirms their participation in the study, their treating physician will be informed of their intentions and given the opportunity to address concerns. A summary of the patient's medical history and cardiac investigations/procedures will be compiled by the chief investigator for the study medical advisor to examine and advise further for inclusion/exclusion on medical grounds. Included participants will then be scheduled to attend their initial baseline testing session, which includes a supervised exercise electrocardiogram. If patients are unable to commit to the study at the initial screening appointment, they will be followed up with a phone call from a member of the research team to confirm participation in the study.

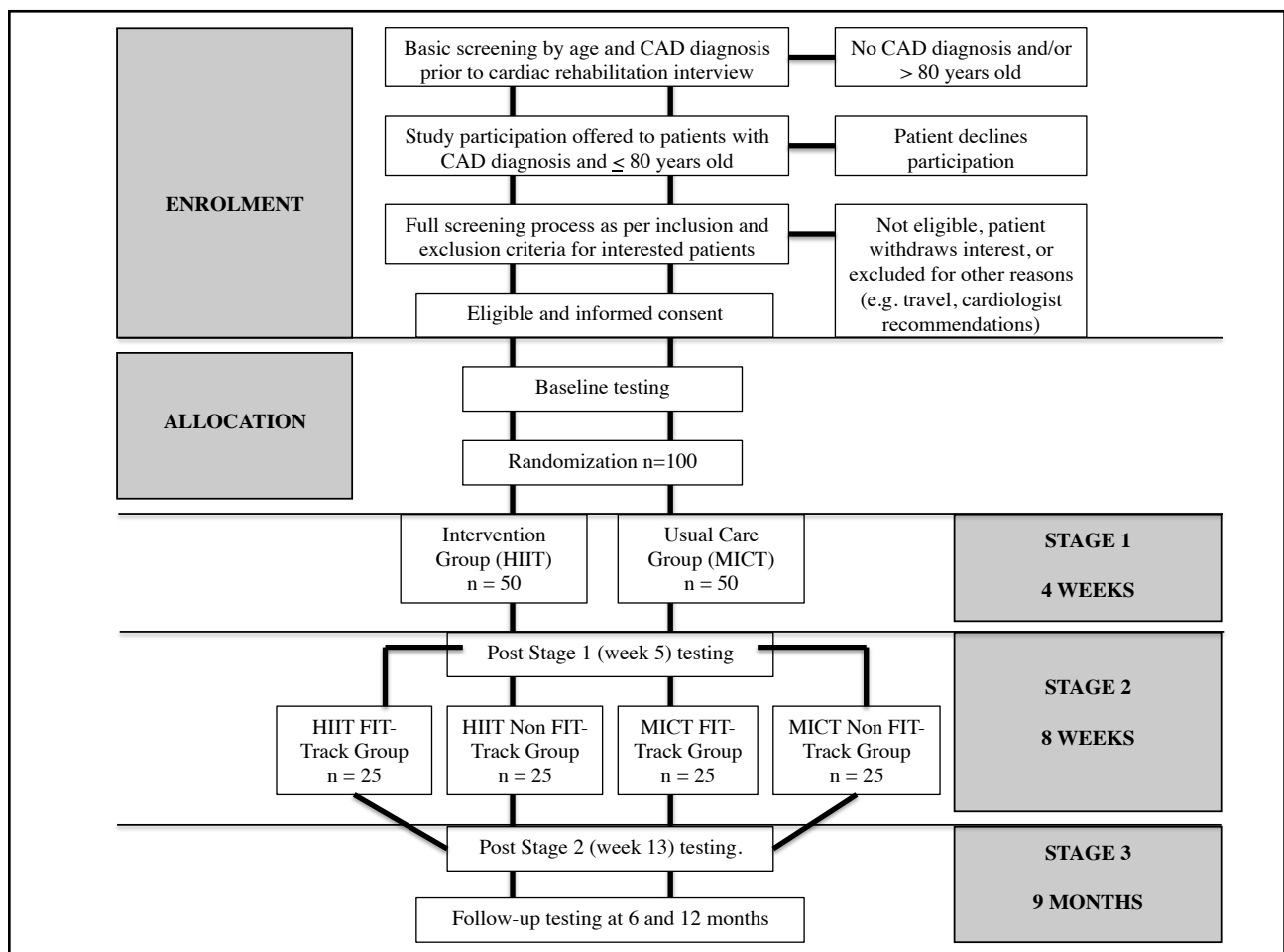


Figure 1: Flow diagram for enrolment, group allocation, and stages in The FITR Heart Study. Abbreviations: CAD, coronary artery disease; MICT, moderate intensity continuous training; HIIT, high intensity interval training; FIT-Track, fitness-tracking

Randomization

Following baseline testing, participants will be randomized to either:

- 1) Intervention exercise group – High Intensity Interval Training (HIIT) or
- 2) Usual care exercise group (control) – Moderate Intensity Continuous Training (MICT).

Prior to Stage 2, all participants will be randomly assigned to either FIT-TRACK or non-FIT-TRACK, which will result in four intervention groups (Figure I). Participants who currently use a fitness-tracking device (within the past month), or do not have access or a computer or smartphone, will be excluded from this randomization and subsequent FIT-Track analysis.

A computerized random number generator will be used to create the randomization sequence, which will be transferred to allocation cards and sealed in sequentially numbered opaque envelopes. To ensure allocation concealment, the randomization sequence will be generated and saved electronically by an individual who is not part of the study team. To ensure homogeneity of groups, the randomization process will involve stratification of participants by initial fitness level and sex. Initial fitness level will be classified as below average (<50% percentile) or above average ($\geq 50\%$ percentile) based on aerobic capacity normative data by Loe et al [30].

Data collection, monitoring, and management

Participants will be assessed at 5 testing periods: baseline (week 0), post-stage 1 (week 5), post-stage 2 (week 13), 6-month follow-up, and 12-month follow-up. MRI scanning will be conducted at baseline and post-stage 2 (week 13). Data will be collected on a case report form at each testing, exercise, or telephone follow-up session. Case report forms will be de-identified, containing only subject ID code. Data required for analysis collected via the case report form, will then be entered directly into SPSS statistics (IBM, New York, USA) software by one operator to reduce potential data error from multiple data entry. Random checks of the SPSS database will be conducted on a regular basis to ensure data has been entered correctly.

Hard copy data (e.g. case report forms, consent forms) will be kept in lockable filing cabinets throughout the study period and 10 years thereafter. Electronic data will be stored within a Trial Master File located on The University of Queensland server. Electronic files will be password protected and only available to members of the investigation team outlined by Human Research Ethics Committee approvals. On completion of the project, de-identified electronic data will be kept in perpetuity to be available for other researchers wishing to conduct systematic reviews or meta-analyses, or used to form a historical cohort for relevant studies.

Exercise protocol

All supervised sessions will be delivered by an Accredited Exercise Physiologist with various aerobic exercise machines used (e.g. treadmill, cycle ergometer, cross-trainer, or rowing ergometer) depending on patient preference and musculoskeletal limitations. Both MICT and HIIT groups will be exercising together in the same class environment with up to 10 patients and 2 instructors per class. The instructors will not be providing any additional motivation or music influences than usual care. During supervised sessions, RPE, HR, and workload will be documented for all participants to monitor adherence to the exercise protocol.

The usual care MICT group, as per current practice, will perform a total 40 minutes of aerobic exercise using various aerobic exercise machines (minimum 20 minutes per machine) at a moderate exercising intensity, corresponding to an RPE of 11-13 (fairly light to somewhat hard) as per the BORG 6-20 scale [31].

The intervention HIIT group will perform a HIIT protocol consisting of 4 x 4 minute high intensity exercise intervals corresponding to an RPE of 15-18 (hard to very hard) as per the BORG 6-20 scale [31], interspersed with 3 minute active recovery intervals corresponding to RPE 11-13. At the beginning of the high intensity interval, participants will be instructed to increase their intensity to an RPE of 15 and then aim to maintain this workload for the 4-minute interval, thereby finishing the high intensity interval at an RPE of 15-18.

HR monitoring

Although RPE will be the primary method for prescribing exercise intensity for both groups, HR will be monitored at each supervised exercise session during Stage 1. Peak HR (HR_{peak}) will be determined by electrocardiography recorded during the peak VO_2 test. Both groups will be provided with a HR range to guide exercise intensity and provide a means of education for RPE. The HIIT group will be given a HR guide of 85-95% HR_{peak} and the MICT group a HR guide of 65-75% HR_{peak} . Therefore participants taking beta-blocker medications are likely to be guided with lower HR ranges, reflective of their lower HR_{peak} during maximal exercise testing. Although HR_{peak} will be provided as a guide for

exercising intensity, participants will be encouraged to use RPE when there is discordance between RPE and HR targets. Using RPE is more commonly used to prescribe exercise intensity in a real world setting, particularly if maximal exercise testing has not been conducted or if dose/timing of beta-blockade medication is different between testing and exercise training. The HIIT group will also be required to monitor and record HR during home-based sessions throughout Stages 1-2 with devices provided (Polar, Polar Electro, Kempele, Finland). No HR monitors will be provided for Stage 3. Participants may purchase their own HR monitor if they desire to continue using HR as a measure of intensity. Otherwise RPE will be used as the sole measure of intensity.

Isoenergetic calculations

The HIIT protocol, similar to that originally described by Rognmo, et al [32], has been formulated to provide an isoenergetic workload (same energy expenditure) as the usual care MICT session. The isoenergetic calculations have been based on work by Rognmo, et al [32] in patients with CAD, with an average peak VO₂ of 2.55 L/min. Both groups will receive the same three minute warm-up and three minute cool down, corresponding to < RPE 11 (fairly light). HIIT participants will perform an additional minute of warm-up at RPE 11-13. Total exercise time will be 26 minutes for HIIT and 34 minutes for MICT, plus 6 minutes total for warm up/cool down for both. For the calculations, an average of 85% peak VO₂ (2.17L/min) has been used for high intensity and an average of 55% peak VO₂ (1.4L/min) has been used for moderate intensity. Therefore total work for HIIT (16min x 2.17 L/min + 10min x 1.4 L/min) = 48.7 L and total work for MICT (34min x 1.4L/min) = 47.6 L, equating to <3% difference between groups.

	MICT	HIIT
Warm-up	3 min at < RPE 11 (Fairly light)	3 min at < RPE 11 (Fairly light) + 1min at RPE 11-13
Exercise component	Various exercise modes Total of 34 minutes moderate intensity exercise at RPE 11-13 (fairly light to somewhat hard)	Various exercise modes 4 x 4 minute high intensity intervals at RPE 15-18 (hard to very hard) interspersed with 3 x 3 minute recovery intervals at RPE 11-13 (fairly light to somewhat hard)
Warm-down	3 min at < RPE 11 (Fairly light)	3 min at < RPE 11 (Fairly light)
Duration	40 minutes	32 minutes
Frequency	3 times per week	3 times per week

Table 2: Structure of exercise training protocols

Abbreviations: MICT, moderate intensity continuous training; HIIT, high intensity interval training; RPE, Rating of perceived exertion

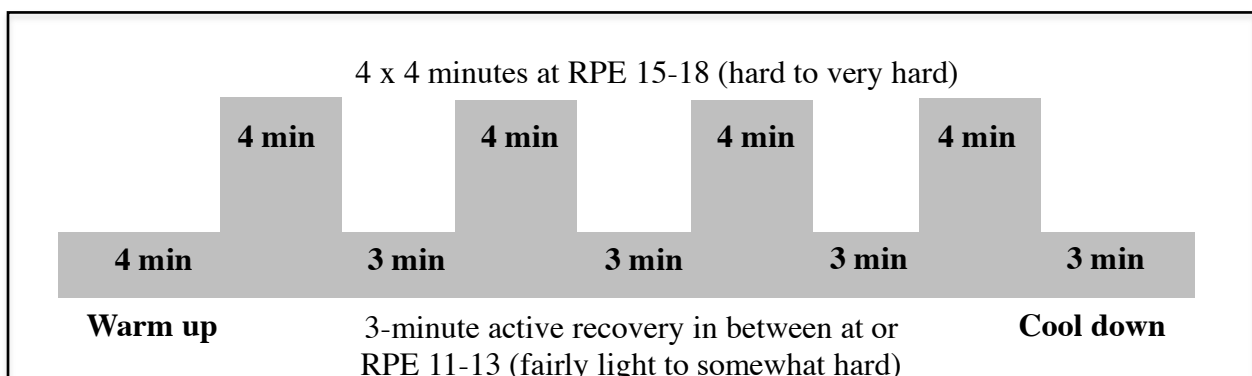


Figure 2: Illustration of the 4 x 4 isocaloric high intensity interval training (HIIT) protocol

Abbreviations: RPE, Rating of perceived exertion

Familiarization of training

At the initial exercise session (Stage 1), participants will receive education about their exercise protocol and monitoring intensity. This will be reinforced throughout the supervised program and participants will receive education on how to progress their exercise to maintain desired intensity. For example, if HR decreases, speed/workload must increase. By teaching participants how to independently manage their exercising protocol and intensity we aim to promote self-efficacy and guide them to feel competent in their exercising ability. Participants will receive support at each supervised exercise session throughout Stage 1 (total of 8) to reinforce the exercise protocol and have the opportunity to raise questions or concerns. Following completion of the 4-week CR program (Stage 1) participants will have a good understanding of how to continue their prescribed training at home for the duration of the study, however routine telephone support will be provided during the initial 8 weeks of home-based program (Stage 2). Participants will also be provided with a Participant Study Manual for additional information relating to their exercise protocol, home-based training, and progressing their training.

Habitual physical activity and dietary behavior

All participants will receive a standard lifestyle education during the CR program (Stage 1) on nutrition, physical activity, and other aspects of self-managing their cardiovascular disease. This will involve presentations and/or printed materials on the following topics: Nutrition for a healthy heart; Portion sizes; Food label reading; Maintaining a healthy weight; and Physical activity. To ensure consistency of education to all participants, printed materials will be provided to all participants at the commencement of the study and a record of each education presentation will be kept and dated as they are completed. Participants will not receive any individualized dietary advice or physical activity advice, other than the prescribed intervention.

During each testing period, energy intake and physical activity will be assessed to account for any differences between groups. Physical activity will be measured by a tri-axial accelerometer (GENEActiv, Activinsights Ltd., Cambridgeshire, UK or ActiGraph, Pensacola, Florida, USA) worn for 7 consecutive days. The type of accelerometer used will remain constant for each participant. In addition, participants will be asked to keep a brief log with details for if the device was removed and time and duration of any exercise training sessions during the monitored period. Time spent in moderate to vigorous physical activity will be determined from the raw accelerometry data using previously developed open source code [33-35]. Additional variables will also be analyzed (e.g. sedentary behaviour) if recommended by current literature at time of analyses. To be included in analysis, participants must wear the monitor for ≥ 16 hours per day, and have a minimum of four valid days, one of which must be a weekend day. Physical activity will also be assessed by self-report, using a modified version of the International Physical Activity Questionnaire.

To measure energy intake, food intake data will be obtained by 24-hour food recall using a multiple pass method [36]. A dietitian or trained nutrition assistant will conduct the 24-hour recall via telephone on multiple days during each testing period. Average daily intake of energy and macronutrients will be calculated by automated software using the Australian Food, Supplement, and Nutrient Database (AUSNUT) [37]. Dietary behavior and food preferences will be assessed by appetite visual analogue scales [38], the 18-Item Three Factor Eating Questionnaire (TFEQ-R18V2) [39-42], and a computer-based food preference questionnaire [43]. The TFEQ-R18V2 is a shortened version of the original TFEQ, which was modified for clinical trials to reduce participant

burden. It has been validated in non-European obese and normal weight populations to measure and characterize dietary behaviors, such as uncontrolled eating (hunger), emotional eating (disinhibition), and cognitive restraint that may influence clinical intervention outcomes [40].

Outcome Measures

Primary Outcome Measure

- Cardiorespiratory fitness (VO_{2peak})

VO_{2peak} and ventilatory efficiency variables (oxygen uptake efficiency slope, ventilatory ratio for carbon dioxide, and oxygen pulse) [11] will be assessed by a graded maximal oxygen uptake test within a medically supervised environment. An individualized ramp protocol will be used, as recommended by Myers et al [44]. Treadmill will be the preferable mode for the test; however, an exercise bike will be available for participants with walking limitations. Regardless of modality, the same apparatus will be used at subsequent testing sessions. Prior to the test, participants will be asked to avoid exercise, caffeine and tobacco for 24 hours, and food for 2 hours, but to take all usual medications. The treadmill protocol (see Table 3) will commence with a 3-minute standing rest period to allow for the measurement of resting pulmonary gas exchange. Warm-up will begin at 4 km/h and 0% gradient for a 2-minute period before increasing to 4% gradient at the same speed for a further 2 minutes. Following the warm-up, participants will perform exercise in continuous 1-minute stages, beginning at a fast walking speed and increasing gradient by 1% each stage until volitional fatigue or other indication for terminating exercise testing in accordance with the American Heart Association guidelines [29]. Speed will increase by 1km/hour every 3 minutes. Fast walking speed chosen at the initial exercise test will be based on 6-minute walk data from the initial CR interview, thereby individualizing the exercise protocol for each participant. If fast walking speed is 4km/h, warm-up speed will be 3km/h. For the bike, warm-up will involve participants cycling at a workload corresponding to an RPE 10 at a speed of 60 revolutions per minute for 4 minutes before the intensity is increased by 25-50 watts for a further 4 minutes. Following warm-up, the intensity will be increased by 25 watts each minute until the test is terminated. Pulmonary gas exchange will be measured from the beginning of the rest period until cessation of the test using a metabolic system (Parvo TrueOne 2400, ParvoMedics Inc., East Sandy, USA or MetaMax3B, Cortex Biophysik, GmbH, Leipzig, Germany). The type of metabolic system used will remain constant for each participant. Simultaneous electrocardiogram recording and analysis will also take place during the test. Blood pressure and RPE will be measured at rest and every 3 minutes from the beginning of warm-up. Heart rate will be monitored by continuous electrocardiography before the test, and every minute during warm-up and the exercise test, at cessation, and in recovery. Blood pressure will also be assessed 1-minute and 5-minutes post-test. VO_{2peak} will be determined from the average of the two highest values attained in 10-second epochs, disregarding outliers when the difference between the two highest VO_2 values is greater than 200ml/minute divided by bodyweight. Ventilatory efficiency variables will be calculated from direct measurements of oxygen consumption, carbon dioxide production, and minute ventilation using previously published equations [45, 46].

Stage	Duration (minutes)	Gradient (%)	Speed (kilometers/hour)
Rest	3	0	Stationary
Warm-up 1-1	1	0	3-4km/hr
Warm-up 1-2	1	0	3-4km/hr
Warm-up 2-1	1	4	3-4km/hr
Warm-up 2-2	1	4	3-4km/hr
1-1	1	5	Fast-walk speed
1-2	1	6	Fast-walk speed
2-1	1	7	Fast-walk speed
2-2	1	8	Fast-walk speed + 1km/h
3-1	1	9	Fast-walk speed + 1km/h
3-2	1	10	Fast-walk speed + 1km/h
4-1	1	11	Fast-walk speed + 2km/h
4-2	1	12	Fast-walk speed + 2km/h
5-1	1	13	Fast-walk speed + 2km/h
5-2	1	14	Fast-walk speed + 3km/h
6-1	1	15	Fast-walk speed + 3km/h
6-2	1	16	Fast-walk speed + 3km/h
7-1	1	17	Fast-walk speed + 4km/h
7-2	1	18	Fast-walk speed + 4km/h
8-1	1	19	Fast-walk speed + 4km/h
8-2	1	20	Fast-walk speed + 5km/hr

*Table 3: Treadmill protocol used for Peak VO₂ testing
Abbreviations: km/h, kilometers/hour*

Secondary Outcome Measures

- Visceral adipose tissue (VAT)

VAT will be measured by a standard 3 Telsa magnetic resonance imaging (MRI) system. Technicians will be blinded to group allocation. Patients will be instructed to lie in a supine position, and a sagittal localizing image will be used to position transverse slices from the diaphragm to pelvis. Axial T1-weighted True Fisp (Fast imaging steady state precession) images will be acquired (TR = 4.45 ms, TE = 1.91 ms, flip angle = 40°) with slice thickness of 5 mm and inter-slice gap of 5 mm. Images will be acquired during suspended end-expiration with breath-hold duration of approximately 10s per acquisition, these images will be used to plan spectroscopy voxel. Axial T2 HASTE (Half Fourier Single-shot Turbo-spin Echo) breath hold will be acquired (TR 2000ms TE 54ms flip angle 90°) with slice thickness of 10mm using body matrix surface coil. Images will be acquired during suspended end-expiration with breath hold 12s per acquisition. Cross-sectional areas of both abdominal VAT and subcutaneous adipose tissue will be measured by semi-automated specialized software. VAT and subcutaneous adipose tissue volume will be calculated by the summation of all VAT and subcutaneous adipose tissue area slices and adjustment for slice thickness and inter-slice gap. This protocol has been adapted from previous work by our investigation team [24].

- Feasibility

Questionnaires have been developed to obtain qualitative and quantitative data about the feasibility of the exercise protocols for CR program staff and participants.

For the staff questionnaire, Likert scale questions will be asked relating to: the ease/difficulty of interpreting and delivering the exercise instructions to patients; any additional burden related to monitoring or encouraging patients throughout the exercise session; and whether they have encountered any patients unable/unwilling to complete the exercise protocol. Qualitative data will also be sought from feedback sections, pertaining to how the exercise protocol could be improved to make it more feasible, and whether there were any specific reasons why patients were unable to complete the protocol. To ensure anonymity for CR staff, all feedback data will be collected by an external research assistant and will be de-identified prior to analysis. HIIT will be deemed feasible if over 70% of questionnaires select “Yes” that HIIT would be feasible as a standard option for appropriate and willing participants, having taken into account all the factors outlined by the questions.

For the participant questionnaire, likert scale questions will be asked relating to: the ease/difficulty and confidence of performing, monitoring, and adhering to the recommended exercise protocol. Qualitative data will also be sought from feedback sections, pertaining to what would help them continue doing the recommended exercise protocol. This feedback will be evaluated throughout the study to ensure barriers to exercise are identified and equally addressed across groups. The exercise protocol will be deemed feasible if over 70% of participants select “Yes” that they would continue to incorporate the exercise protocol as part of their regular exercise routine.

- Safety

Safety will be assessed using data collected on adverse effects, which will be monitored throughout the study and recorded by an Adverse Events Log. The type, incidence, and severity of adverse events (Grade 1: Mild; Grade 2: Moderate; Grade 3: Severe; Grade 4: Life-threatening; and Grade 5: Death) will be recorded. Adverse event rates will be assessed and graded by medical staff, and reported per number of training hours, before a comparison between MICT and HIIT groups is made. Events per number of training hours will be reported and compared to published event rates from other exercise studies.

Participants will be advised to report and log any adverse event that may occur during the study. They will be provided with contact details for reporting and an adverse event log. In addition to self-report, participants will be questioned weekly about adverse events during Stage 1 and Stage 2, and at the 6 month and 12 month follow-up during Stage 3.

- Exercise adherence

Exercise adherence will be assessed as 1) completion of the recommended number of supervised and home-based sessions per week and 2) as the ability to achieve the prescribed intensity and duration of exercise sessions. Successful exercise adherence involves achieving at least 70% of the randomized exercise protocol targets during each study stage. As this study will use an intention to treat analysis, all participants (even if deemed non-adherent) will be encouraged to complete all testing sessions. Intention to treat analysis is described in more detail below.

A combination of physical attendance, self-reporting, and activity device data will be used to assess exercise adherence. For self-reporting, participants will be asked to keep an exercise training record during Stage 1 and 2 of the study. During Stage 1, exercise adherence will be recorded on the

exercise data sheets at supervised exercise sessions and participants will submit their exercise training record on a weekly basis. During Stage 2, participants will continue to submit their exercise training record on a weekly basis via email. For those participants in the FIT-TRACK group, extracted data will also be used to assess adherence to the duration, frequency, and intensity of exercise sessions. During Stage 3, exercise adherence will be self-reported by participants during their 6 month and 12 month follow-up sessions.

- Body composition

Dual-energy x-ray absorptiometry (DEXA) (Dephi X-Ray Bone Densitometer, Hologic Inc., Bedford, USA) will be used to measure body composition (total bodyweight, total body lean tissue mass, total body fat mass, total body fat percentage and total body bone mineral content). An advantage of DEXA is the quantification of total lean muscle mass and bone mineral content, which cannot be obtained from abdominal MRI. Advanced DEXA software (APEX Version 4.5.3, Hologic Inc.) will also provide an estimate of total VAT, which may be useful for testing periods without MRI (post-Stage 1, 6 month, 12 month) once comparisons have been made at baseline testing. However, there is limited evidence for the repeatability of VAT estimation from DEXA compared with gold standard methodology. Therefore accuracy of DEXA VAT estimations compared with MRI over repeated measures will be conducted using data from baseline and post-Stage 2 (week 13) testing periods. To measure repeatability of DEXA VAT estimation, a repeat DEXA scan will be performed on each subject during the baseline testing period. Waist circumference will be measured according to International Society for the Advancement of Kinanthropometry Standards [47]. Measure taken via tape in the horizontal plane at the narrowest point between the inferior margin of the ribs and the superior border of the iliac crest following expiration. If there is no obvious narrowing the measurement is taken at the mid-point between the lower costal (10th rib) border and the iliac crest. Stature will be measured to the nearest millimetre by stadiometer and bodyweight will also be assessed and recorded to the nearest gram.

- Blood analysis

Up to 24ml of venous blood will be collected into plasma (with anticoagulant agent) and serum (with clot activator) vacutainers from the antecubital vein according to standard phlebotomy procedures. Participants will be instructed to fast overnight (≥ 12 h), and avoid exercise, caffeine, alcohol, and tobacco for 24h. Plasma vacutainers will be placed on ice immediately following collection and centrifuged within 10 minutes. Serum vacutainers will be kept at room temperature for 30 minutes after collection. Samples will be centrifuged for 10 minutes at 4°C and 3000rpm. After centrifugation, samples will be divided into aliquots of plasma and serum and then stored in an organized freezer box system at -80°C for later analysis. Prior to centrifugation, the plasma sample will be assessed for hemoglobin using an autohaematology analyzer (BC-5150, Shenzhen Mindray Bio-Medical Electronics Co Ltd., Shenzhen, China), to monitor for any effect on changes in peak VO_2 . The lipid profile will include assessment of total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides using Randox (Randox Laboratories, Crumlin, UK). Detection and quantification of plasma insulin will be performed using a radioimmunoassay Cobas 3411 (Hitachi High-Technologies Corporation, Tokyo, Japan) or Magpix (Luminex Corporation, Austin, USA) analyzer. The homeostasis assessment model will be used to estimate insulin resistance. High-sensitivity C-reactive protein will be assessed using Randox (Randox Laboratories, Crumlin, UK) or Cobas Mira (Roche Diagnostics, Australia) analyzers. Inflammatory adipokines

(leptin, adiponectin, tumor necrosis factor- α , interleukin-6), and appetite hormones (ghrelin and peptide YY) will be assessed using specific ELISA kits (R&D system Inc. Minneapolis, USA) or Magpix (Luminex Corporation, Austin, USA) analyzer. All assessments will be performed in duplicate.

- Vascular structure and function, and heart rate variability

Measurements will be performed after an overnight fast (≥ 12 h), with participants instructed to avoid caffeine, alcohol, tobacco, and strenuous exercise for 24 hours. A seated blood pressure will be measured manually on each arm. When there is a difference >10 mmHg between arms, a third measure will be taken on the arm with the highest reading. After fifteen minutes of supine rest, heart rate variability will be measured using continuous electrocardiogram recorded for five minutes. Pulse wave analysis and pulse wave velocity will then be measured using automated technology (SphygmoCor, AtCor Medical Pty Ltd., West Ryde, Australia). For pulse wave analysis, a cuff will be placed around the arm, between the elbow and shoulder, and will be partially inflated to obtain the augmentation index. For pulse wave velocity, a cuff will be placed around the femoral artery to capture the femoral waveform, and a tonometer pressure sensor on the carotid artery to capture carotid waveform. The velocity of pulse transfer from the carotid artery to the femoral artery will be measured. Pulse wave analysis and pulse wave velocity will be each assessed three times. Endothelial function will be assessed as flow-mediated dilation (FMD) using high-resolution vascular ultrasound (Usmart 3300, Teratech Corporation, Burlington, USA) in accordance with guidelines for a nitric oxide dependent approach [48]. A 7.5Hz probe will be used to capture B-mode images of the brachial artery in the right arm. The probe will be placed on the distal third of the upper arm (proximal to the antecubital fossa) and orientated to the longitudinal plane. Following image optimization, continuous images will be recorded to measure vessel diameter and blood velocity, using the lowest possible insonation angle (≤ 60 degrees). Baseline images will be continuously recorded for 1 minute to capture diameter and velocity. A sphygmomanometer cuff, placed directly distal to the olecranon, will be subsequently inflated to 220mmHg (or 50mmHg above systolic blood pressure). The cuff will remain inflated for five minutes, with continuous recordings of the brachial artery commencing 30 seconds before deflation, and for three minutes thereafter. Hyperemic velocity will be assessed via mid-artery pulsed Doppler signal obtained upon immediate release of the cuff. All recordings will be analyzed offline by specialized, automated edge detection and wall tracking software to provide an objective measure of peak diameter and calculation of shear rate as previously described [49]. Arterial diameter, flow and shear rate will be analyzed using the 1-minute baseline recording prior to cuff inflation and 3-minute recording following cuff deflation. FMD response will be reported as absolute (in millimeters) and relative (in %) change in post-stimulus brachial artery diameter from baseline diameter. Shear rate stimulus (area under the curve until peak diameter) will also be reported. Clinical significance has been reported to be as small as 1%, with a meta-analysis reporting 8% increased cardiovascular event risk for 1% decrease in FMD, after adjusting for traditional risk factors [50].

- Intrahepatic lipid

Intrahepatic lipid will be measured by proton magnetic resonance spectroscopy (^1H -MRS) during the MRI procedure previously mentioned. Intrahepatic lipid concentration and composition will be measured using the protocol outlined by Johnson, et al [51]. Image-guided, localized ^1H -MRS will be acquired from a voxel of 3.0 x 2.0 cm x 2.0 cm using the whole-body (Q body) transmit coil

body matrix surface coil (flex 6-channel surface) receive coil, with volumes of interest centered within the right lobe of the liver. Subjects will lay supine, with spectra acquired during respiratory gating (end-expiration). Spectra will be acquired using the PRESS (point resolved spectroscopy) technique (TR = 2000 ms, TE = 30 ms, 32 measurements, 2048 sample points). A similar voxel placement will be facilitated between measures within-individual, guided by image capture at the baseline measurement and replicated as closely as possible. Fully automated advanced shimming will be performed on the volume of interest to ensure maximum field homogeneity. Excitation water suppression will be used to suppress the water signal during data acquisition with unsuppressed water spectra acquired in vivo for use as the internal standard. Breath-hold spectroscopy (four averages, 12s per acquisition) will also be acquired. Data will be processed by magnetic resonance user interface software. For hepatic lipid concentration and composition, a five resonance model will be employed [51]. Hepatic water signal amplitudes will be measured from the non-water suppressed spectrum using Hankel Lanczos Squares Singular Values Decomposition.

- Quality of life and exercise enjoyment

A revised 8-item version of The Physical Activity Enjoyment Scale [52] will be used to assess participants' enjoyment of the exercise intervention. The MacNew Heart Disease health-related quality of life instrument will be used to assess the impact of the exercise interventions on participants' quality of life across physical, emotional, and social domains. The MacNew has a low respondent burden taking on average 10 minutes or less to complete [53].

Blinding

For peak VO₂ testing, the medical advisor and technician providing the encouragement and motivation will be blinded to group allocation. All MRI technicians will be blinded to group allocation.

Monitoring and reporting adverse events

Monitoring and recording of adverse events has been previously outlined as per measure of safety. If an adverse event or other medical concern (e.g. abnormal electrocardiography) occurs during the maximal exercise test, this will be communicated to the treating physician. For serious adverse events, an ambulance will be contacted and basic life support provided.

For serious adverse events that occur during supervised exercise sessions at the hospital, a Code Blue – Medical Emergency will be called and medical assistance will be provided promptly. The adverse event will then be reported to the hospital quality and safety department.

All serious adverse events will be reviewed by a medical advisor and reported to the ethics committees within 24 hours. In the event that illness, injury, or other adverse event limits a participant from successfully adhering to their exercise protocol during Stage 1 (> 70% recommended sessions), a make up period of 8 sessions will be required within a 4 week period before post-Stage 1 (week 5) testing will be performed.

Sample size calculations

The sample size calculation for peak VO₂ was conducted using the change over the four week supervised phase of the CR program, the primary outcome of this study. This timeframe was selected as it represents a standard CR program. Measurements post-Stage 2 (13 weeks), and at 6- and 12-month follow-up, will be secondary outcomes. The sample size calculation was for change

in VO_{2peak} (ml/kg/min) between the two groups. A clinically significant change was taken as 1 MET (3.5ml/kg/min) based on the work of Kodama et al [54], which indicated this would reduce the risk of cardiovascular disease and all cause mortality by 15% and 13% respectively. It was assumed that the standard deviation of the change in VO_{2peak} would be 4.75ml/kg/min, based on the work of Moholdt et al. in 59 patients post CABG [55]. Therefore with power of 0.9 and a 0.05 level of significance, 80 participants would be required. Accounting for a 20% loss to follow-up, a total of 100 participants will be recruited.

Statistical analysis

All statistical analyses will be carried out on an intention- to-treat basis unless otherwise stated. Continuous variables will be described using mean (standard deviation) or median (interquartile range), while categorical variables will be described using frequencies (percentages). Though our design will randomly assign participants, we will assess any possible imbalances in baseline variables between HIIT and MICT groups that could potentially affect the impact of HIIT intervention on the outcomes. Pearson's Chi-square test or Fisher's exact test will be applied to assess categorical variables. Depending on normality, student's *t*-test or the Mann–Whitney *U*-test will be applied to assess continuous variables. Continuous outcomes including the primary outcomes of peak VO_2 and VAT will be analyzed using random effects multivariable linear regression, while categorical outcomes will be analyzed using random effects multivariable logistic regression [56]. Conditional on the degree of dispersion, either mixed effects poisson or negative binomial regression will be used to model count data [57, 58]. Irrespective of modeling approach, correlation of observations within participants and over follow-up will be accounted for by the inclusion of random intercepts and slopes into the regression modeling. All models will treat intervention as a fixed effect and adjust for all possible measured confounders. To test whether intervention effect will be modified by the presence of model covariates, all models will be extended to include the presence of interaction terms. Sensitivity analyses will be conducted testing model functional forms, the variables to be used, and the impact of influential outliers on estimates. In addition, per-protocol analyses will also be conducted to assess the robustness of our findings for various degrees of non-adherence and protocol violation. Where appropriate and under the assumption of missing at random, multiple imputation will be used to account for missing data, with results being compared to those produced by complete case analyses [59]. All analyses will be conducted using SPSS Statistics (IBM, New York, USA) or Stata (Texas, USA). The level of statistical significance will be set at 0.05 and all hypothesis tests will be two-sided. Regarding missing data, our study will operate in line with the principles of good clinical practice [60]. We will invite all participants who drop out of the intervention to complete the final outcome assessment measures and subsequently complete an intention to treat analysis. Those who do not wish to partake in these final outcome assessments will be asked to complete a study withdrawal form and in instances where this form is not completed, the participant will be considered 'lost to follow up'. An analysis will be run with and without multiple imputations for missing data. If outcomes of these analyses are comparable, suggesting that the data is missing completely at random, we will run the analyses without imputation. If the analyses are not comparable, our analyses will be run with the multiple imputation method for missing data.

Discussion

Cardiorespiratory fitness:

Cardiorespiratory fitness is a strong predictor of mortality and more cardioprotective than overall physical activity levels [61]. For patients attending CR, each 1ml/kg/min increment in peak VO_2 has been equated to a 9% improvement in cardiovascular prognosis [5]. Furthermore in primary prevention of heart disease, other measurements of exercise capacity, estimated metabolic equivalents (METs), have been strongly associated with a 25% reduced risk of cardiovascular events [62] and 16% improvement in survival, for every 1-MET increase in cardiorespiratory fitness [63]. We recently demonstrated that HIIT improves peak VO_2 by double that of MICT in cardiometabolic disease, making it an effective way to improve outcomes in chronic disease groups [9]. Previous studies have alluded that the superior improvements in peak VO_2 seen with HIIT are due to the potent exercise stimulus provided during the high intensity interval periods. Higher intensities are thought to invoke greater aerobic and cardiovascular adaptation than low to moderate intensities. It is unlikely the work rate required to create this potent stimulus can be performed in a continuous manner. Duration of the interval also appears to be important with 4-minute HIIT protocols [20, 32, 64] producing superior improvements in peak VO_2 to MICT, as opposed to comparable improvements in studies employing 2-minute HIIT protocols [65].

Visceral adipose tissue (VAT):

VAT is an active endocrine organ releasing proinflammatory mediators (adipokines) that directly contribute to vascular injury, insulin resistance, and atherogenesis [66]. Elevated VAT levels can exist even in normal weight individuals, a concept known as the metabolically obese normal weight [67], and is associated with increased risk of atherosclerosis [68]. Interval training protocols of varying nature have shown that significant reductions in VAT can occur in the presence [25] or absence [26-28] of changes in body mass and waist circumference. Furthermore HIIT has been shown to be superior to MICT for reducing VAT in overweight females despite similar reductions in total body fat [69]. The absence of change in standard body composition measures (such as body mass, waist circumference, and total body fat percentage) poses some difficulty in measuring the effectiveness of interventions on VAT reduction. Few studies exist comparing the effects of exercise intensity on VAT using gold standard medical imaging techniques such as computed tomography or MRI, presumably due to the significant expense of this assessment and radiation associated with computed tomography. While studies have validated DEXA to provide an accurate estimate of VAT compared to single [70] and multiple slice [71] computed tomography, further research is warranted to assess the reliability of VAT estimation by DEXA overtime with changes in regional fat loss.

The feasibility of HIIT in a cardiac rehabilitation setting:

Although HIIT is well established as standard care in many CR centres across Norway [72], there is a paucity of data on the integration of HIIT into CR programs in other countries, with only one study outside of Europe [64]. This study concluded HIIT was successfully integrated into their CR setting and produced greater improvement in peak VO_2 compared to MICT [64]. Informal feedback from staff and participants highlighted there were no concerns associated with the integration of HIIT, including the monitoring and progressing of workloads, and that HIIT participants found the exercise more enjoyable and “less boring”. This is consistent with other studies reporting HIIT to be

more enjoyable than MICT [73], and HIIT resulting in greater improvements in quality of life [9, 74]. Historically, studies investigating the feasibility of exercise interventions have used quantitative outcomes such as: study recruitment rate; adherence and compliance to the exercise protocol; enjoyment of the exercise protocol; study attrition rate; and adverse events [75]. To our knowledge no study has published qualitative data on feasibility of HIIT, highlighting attitudes and feelings about performing (for patients) or prescribing (for staff) HIIT in a real world setting. Feasibility issues may include: confidence of CR staff in delivering and monitoring HIIT; the ability and confidence of patients to self-monitor their exercise intensities; and the practicality of mixing of different exercise protocols (HIIT and MICT) within the same class environment.

The safety of HIIT in patients with cardiovascular disease:

The safety of HIIT in a CAD population was studied by Rognmo *et al* [72] across three Norwegian CR centres (n=4846). The study indicated the risk was low for both HIIT and MICT, with only one fatal cardiac arrest in 129 456 hours of MICT and two non-fatal cardiac arrests in 46 364 hours of HIIT [72]. Similarly, a meta-analysis by Weston and colleagues concluded HIIT can be a safe option for high-risk patients with appropriate screening and communication with a patient's doctor [9]. More recently a meta-analysis concluded HIIT has a slightly elevated risk of 8% [76]. However, on close analysis of individual events only one of the 13 adverse events occurred during HIIT protocols of 80-95% peak HR/maximal workload. The other 12 adverse events occurred during maximal exertion protocols involving 'all out' sprint interval training >100% of maximal workload.

Adherence to HIIT in clinical populations:

Supervised programs in CAD populations have shown similar attendance rates (>85%) [9] and attrition rates for HIIT and MICT (11% and 12%, respectively) [77]. For home-based programs following a supervised period, HIIT participants have shown greater adherence than MICT participants (89% and 71%, respectively) [78]. Long-term adherence to a home-based HIIT exercise program post CR has only been investigated in a single study cohort [55]. Moholdt *et al.* showed that HIIT and MICT had similar adherence rates at 6 months [55], but HIIT had superior adherence than MICT at 30 months [79]. An emerging area of research is the use of technology for enhancing exercise adherence [80]. A systematic review in patients with type 2 diabetes concluded that the use of personalized web-based programs and professional feedback (e.g., telemonitoring) was effective in enhancing exercise adherence and sustainability [81]. Given that long-term adherence is essential for the continued health benefits of exercise, qualitative research investigating why HIIT may improve exercise adherence long-term is warranted, and whether technology in the form of HR wrist monitors with the ability to upload data to a website for health professional tracking and feedback could be a viable option [80].

The efficacy of HIIT for other cardiometabolic health targets:

Beyond improvements in cardiorespiratory fitness, HIIT has consistently shown superior effects, when compared with MICT, on the lipid profile, and insulin resistance [9, 77]. Additionally, adaptations of skeletal muscle, myocardium, and vascular function, such as mitochondrial biogenesis, left ventricular ejection fraction, and nitric oxide availability, appear to be enhanced by HIIT [9, 77]. A recent meta-analysis by Ramos and colleagues reported a significantly superior

improvement in brachial artery FMD, a non-invasive measure of vascular function, for HIIT (mean improvement 4.31%) vs MICT (mean improvement 2.15%) [82].

The effect of HIIT versus MICT on total fat loss remains equivocal with studies showing a greater effect of HIIT [83-85], a greater effect of MICT [86, 87], or comparable effects [69, 88-92]. Conflicting results may be due to a number of factors such as individual variability of fat loss, greater initial fat levels, and the heterogeneity of interval training interventions, in terms of interval duration and total workload. Potential mechanisms for HIIT eliciting superior fat loss have been proposed [93], including decreased post-exercise appetite. Recently, studies have shown HIIT may improve appetite regulation following 4 weeks [94] and 12 weeks of training [92].

Conclusion

Further research into the feasibility, safety, and long-term adherence of HIIT is necessary to evaluate whether the current research findings can translate into clinical practice. This protocol describes a study investigating the clinical application of HIIT compared to MICT in a hospital-based CR program relating to safety, feasibility, exercise adherence, and efficacy for improving cardiorespiratory fitness and other cardiometabolic outcomes. We expect HIIT will be feasible and safe to incorporate into a hospital-based CR program and will improve patient's exercise adherence long-term. Similarly, we expect that HIIT will result in greater improvements in exercise capacity and other cardiometabolic outcomes. If our hypotheses are supported, our findings will assist in addressing the ongoing concerns regarding the practicality and safety of HIIT in clinical populations such as CAD [95]. We anticipate study findings will lead to the development of a protocol to guide CR programs on how to incorporate HIIT as a standard exercise option for appropriate patients. To our knowledge, this will be the first study in a CAD population to investigate the effect of HIIT and MICT on reducing VAT, which is now understood to play a central role in the pathophysiology of atherosclerosis. Improvements in cardiorespiratory fitness, VAT, and vascular function have the potential to translate into clinically important endpoints such as reducing cardiovascular mortality, hospital readmission, non-fatal cardiovascular event, or coronary revascularization.

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