Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

A detailed description of the design, eligibility, and outcome measures of The FITR-Heart Study: **F**easibility, safety, adherence, and efficacy of high intensity **I**nterval **T**raining in **R**ehabilitation for coronary **Heart** disease, has been previously published [1]. This trial adhered to the Helsinki Declaration and was approved by The University of Queensland and UnitingCare Health Ethics Committees. It was prospectively registered at anzctr.org.au on 26 November 2015 (identifier: ACTRN12615001292561).

Participants

All patients presenting for CR at a single tertiary hospital (The Wesley Hospital, Brisbane, Australia) following diagnosis of CAD, acute coronary syndrome (> 4-weeks), percutaneous coronary intervention (> 3-weeks), or coronary artery bypass graft surgery (CABG) (>4-weeks) were considered for inclusion in the study. Eligible patients were invited to participate at their initial CR appointment. Inclusion criteria [1] included: angiographically-proven CAD (determined by the treating physician), age of 18-80 years, and eligibility to participate in the private hospital CR program. Patients were excluded from participation if they had any absolute or relative contraindications to exercise testing as per the American Heart Association guidelines [2], 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); orthopaedic/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 randomised 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 from; and pregnancy or expecting to be pregnant during the study period.

Randomisation

Patients were randomized 1:1 to 1) HIIT or 2) MICT (usual care), with stratification for baseline fitness level and sex. The randomised sequence was computer-generated and sealed in sequentially numbered opaque envelopes by an individual external from the investigation team. A study investigator then enrolled participants and assigned them to interventions as per the numbered envelopes.

Study design

The study involved three stages: 1) a 4-week supervised program including two supervised and one home-based exercise training sessions per week; 2) a further 2-months of unsupervised home-based training of at least three sessions per week (with weekly support); and 3) a further 9-months of unsupervised home-based training of at least three sessions per week (with informal support only). Weekly support involved submission of exercise logs by the participant and phone/email follow-up by the study team. Study testing occurred at The University of Queensland (Brisbane, Australia) at baseline, 4-weeks, 3-months, 6-months, and 12-months.

Exercise protocols

The HIIT protocol[1,3] involved 4 x 4-minute high intensity intervals corresponding to an RPE 15-18 as per Borg's rating of perceived exertion (RPE) 6-20 scale[4], interspersed with 3-minutes active recovery intervals (RPE 11-13), for a total duration of 32-minutes. The MICT protocol involved usual care exercise, of 40-minutes moderate intensity exercise at an RPE 11-13[11]. Protocols were designed to be isocaloric as previously described[1]. To improve the clinical application of this research, the study focused on using subjective measures of exercise intensity (RPE), as this approach is commonly used in CR programs. Subjective measures of exercise intensity are less affected by alterations in medical therapy (i.e. β-blockade), and do not require re-calibration with improved levels of fitness over the study period[1,3]. Furthermore, objective measures of exercise intensity in CR, such as percentage of maximum heart rate (%HR_{max}), have limited applicability for centres without access to maximal exercise testing facilities. Consequently, the CR clinicians were instructed to use RPE for individual exercise prescription and exercise was progressed gradually to maintain the desired RPE. Participants were also provided a HR range that corresponded to the respective target RPE, in order to reinforce adherence with the exercise intensity. The HR range for the HIIT group was 85-95%HR_{peak} and 65-75%HR_{peak} for the MICT group. Exercise intensity was recorded as average training RPE, peak training RPE, average training %HR_{peak}, and peak training %HR_{peak} as previously suggested[3]. The intensity during the recovery intervals were not monitored. To prevent overestimation of training intensity, %HR_{peak} was calculated from the CPET with highest HR_{peak} attained over the 12-months, unless the change in HR_{peak} was associated with adjustments to β-blocker therapy. Training

HR was measured by 3-lead electrocardiography or pulse oximetry at least 10-minutes into the exercise session. In order to assess adherence to the prescribed intensity, HIIT participants were also provided with HR monitors to record their highest HR for each high intensity interval. All supervised exercise sessions were performed during standard CR exercise classes at The Wesley Hospital (Brisbane, Australia). Both HIIT and MICT groups exercised in the same class environment with a staff to patient ratio of 2:10. A variety of aerobic exercise machines were used according to participant preference or physical limitation[1] (e.g. treadmill, cycle ergometer, elliptical machine, rowing ergometer). Home-based exercise sessions were performed by participants individually in their own environment. They were encouraged to continue with outdoor walking exercise or use personal exercise equipment in their home or commercial gym (e.g. bike, treadmill). No exercise equipment was provided with the exception of a HR monitor for the HIIT group (for stages 1 and 2) to assess whether HR achieved with home-based training was similar to supervised training. The MICT participants were not provided with HR monitors in line with the usual care approach in the CR program. Therefore, training HR was only recorded in the HIIT group during stage 2. RPE remained the primary method of exercise prescription in both groups and the ongoing feedback between the participants and the clinicians/study team was the same in both groups. During the time-frame from 3-months to 12-months neither group was provided with a HR monitor and neither group received formal feedback or support.

Outcome measures

Detailed descriptions and methods for primary and secondary outcomes have been previously published[1]. For measurement of VO_2peak, maximal CPET with electrocardiogram was performed on a treadmill using an individualized protocol [1]. The personnel providing CPET motivation was blinded to the randomisation group. VO_2peak was determined from an average of the highest two values from 10 second epochs during the exercise test. VO_2peak (L/min) was normalized for bodyweight (expressed as mL/kg/min) to better facilitate comparison between subjects of varying body mass[5]. Adjustment of VO_2peak for lean body mass (expressed as ml/kg LBM/min) was also made, as adipose tissue consumes a relatively smaller amount of oxygen than muscle during exercise and normalizing for total bodyweight may be misleading in an overweight population [5]. Ventilatory efficiency was assessed from maximum oxygen uptake efficiency slope (OUES) [6]. Peak oxygen pulse (O_2 pulse) was calculated as VO_2peak (ml/min) divided by peak HR (HRpeak)[5] and relative peak O_2 pulse as VO_2peak (ml/kg/min) divided by HR_{peak} and multiplied by 100 [7]. Exercise capacity in metabolic equivalents (METs) was calculated from the FRIEND registry equation using treadmill speed and grade at peak exercise [8]. Tri-axial accelerometers, were used to measure daily minutes spent in moderate vigorous physical activity (MVPA) ≥1-min bouts, average daily acceleration ('ENMO') [9] and minimum daily acceleration for the most active 30 minutes, with open source code used for analysis [9,10]. For MVPA, specific thresholds were used for the wrist (100mg) or hip (70mg) [11].

Safety was assessed continuously throughout the study period as frequency, type, and severity of serious adverse events (SAE's). All SAE's were referred to the study medical advisor and patient's physician, with simultaneous referral to the independent ethics committee who acted as a safety authority. Adherence to the exercise protocol is presented as the percentage of participants with ≥ 70% attendance at the recommended number of exercise sessions and training at the prescribed exercise intensity prescription during the exercise sessions. Participants were deemed to be training at the prescribed intensity, if for MICT they maintained an average RPE between 11-13 during the session; and for HIIT they maintained an average RPE ≥15 and/or HR ≥85%HR_{peak} during the high intensity intervals.

Statistical analysis

The sample size calculation conducted for the primary outcome, the comparison of groups for change in VO_2peak over a 4-week supervised program, determined 80 participants (40 per group) would be sufficient to detect a 1 MET (3.5ml/kg/min) difference between groups with a standard deviation of 4.75/ml/kg/min, power of 0.9, and 0.05 significance level[1]. For all outcomes, intention-to-treat analyses using linear mixed modelling were performed to investigate the interaction of time and group effects. Time and group were included as fixed effects and subject was included as the random effect. The interaction effect was investigated for the supervised study period (baseline to 4-weeks) and the entire 12-month period (all time points). Data regarding baseline characteristics and exercise adherence were compared using a student's *t*-test for continuous variables and Fisher's exact test for categorical data. Pre-specified per-protocol analyses were conducted including only participants meeting the criteria for exercise adherence[1]. Sensitivity analyses were conducted to account for the effect of medication changes with: (a) the inclusion of relevant medications as covariates, and b) the exclusion of participants with changes to relevant medications.

References for eMethods

1. Taylor J, Keating SE, Leveritt MD, Holland DJ, Gomersall SR, Coombes JS. Study protocol for the FITR Heart Study: Feasibility, safety, adherence, and efficacy of high intensity interval training in a hospital-initiated rehabilitation program for coronary heart disease. *Contemp Clin Trials Commun.* 2017;8:181-191.
2. Fletcher GF, Ades PA, Kligfield P, et al. Exercise Standards for Testing and Training: A Scientific Statement From the American Heart Association. *Circulation.* 2013;128(8):873-934.
3. Taylor JL, Holland DJ, Spathis JG, et al. Guidelines for the delivery and monitoring of high intensity interval training in clinical populations. *Prog Cardiovasc Dis.* 2019;62(2):140-146.
4. Borg G. *Borg's perceived exertion and pain scales.* Champaign, IL, US: Human Kinetics; 1998.
5. Forman DE, Myers J, Lavie CJ, Guazzi M, Celli B, Arena R. Cardiopulmonary exercise testing: relevant but underused. *Postgrad Med.* 2010;122(6):68-86.
6. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol.* 1996;28(6):1567-1572.
7. Laukkanen JA, Araújo CGS, Kurl S, et al. Relative peak exercise oxygen pulse is related to sudden cardiac death, cardiovascular and all-cause mortality in middle-aged men. *Eur J Prev Cardiol.* 2018;25(7):772-782.
8. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. New Generalized Equation for Predicting Maximal Oxygen Uptake (from the Fitness Registry and the Importance of Exercise National Database). *Am J Cardiol.* 2017;120(4):688-692.
9. van Hees VT, Fang Z, Langford J, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol.* 2014;117(7):738.
10. van Hees VT, Gorzelniak L, Leon ECD, et al. Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. *PLos One.* 2013.
11. Hildebrand M, VT VANH, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc.* 2014;46(9):1816-1824.

eTable 1. Medication adjustments throughout the study period

Medication Adjustments	4 weeks		3 months		6 months		12 months		Total	
Group (n)	HIIT (43)	MICT (44)	HIIT (37)	MICT (40)	HIIT (37)	MICT (39)	HIIT (34)	MICT (37)	HIIT	MICT
Medication ceased										
β -blocker	3	1	0	0	0	0	2	1	5	2
ACE inhibitor	0	2	0	0	0	0	0	0	0	2
Diuretic	2	0	1	0	0	0	0	0	3	0
Statin	0	1	1	0	0	0	0	0	0	2
Aspirin	0	2	0	0	0	2	1	0	1	4
Anti-platelet	0	1	0	0	1	1	9	8	9	9
Anti-arrhythmic	0	1	0	0	0	0	0	1	0	2
Total ceased	5	8	2	0	1	3	12	10	20	21
Medication added										
β -blocker	0	0	0	1	0	0	0	0	0	1
Calcium channel blocker	0	0	0	0	0	0	1	0	1	0
Angiotensin II receptor blocker	0	0	0	0	1	0	0	0	1	0
Diuretic	0	0	0	0	0	1	0	0	0	1
Anti-platelet	0	0	1	0	0	0	0	0	2	0
Anti-coagulant	0	1	0	0	0	1	0	0	0	2
Non-statin cholesterol lowering	2	0	0	1	0	0	1	3	2	4
Oral hypoglycaemic	1	0	0	0	0	0	0	0	1	0
Total added	3	1	1	2	1	2	2	3	7	8
Medication decreased										
β -blocker	1	2	1	0	0	1	1	0	3	3
ACE inhibitor	1	0	1	0	0	0	0	0	0	2
Angiotensin II receptor blocker	0	1	2	0	1	0	1	0	4	1
Diuretic	0	0	0	1	0	0	0	0	0	1
Statin	0	1	0	0	0	1	1	2	1	3
Aspirin	0	1	0	0	0	0	0	0	0	1
Total decreased	2	5	4	1	1	2	3	2	10	10
Medication increased										
β -blocker	0	3	1	0	0	0	0	1	1	4
ACE inhibitor	0	1	0	0	0	0	0	0	0	1
Angiotensin II receptor blocker	1	0	0	0	0	1	2	1	2	2
Statin	0	0	1	1	0	1	1	2	0	5
Anti-coagulant	0	1	0	0	0	0	0	0	0	1
Total increased	1	5	2	1	0	2	3	4	6	12
Medication type changed										
β -blocker	0	0	0	1	0	0	1	1	1	2
ACE inhibitor	0	0	1	0	0	0	0	0	1	0
Statin	0	1	0	1	0	2	0	0	0	4
Anti-platelet	0	0	0	0	0	1	0	0	0	1
Oral hypoglycaemic	0	0	0	1	0	0	0	0	0	1
Total type changed	0	1	1	3	0	3	1	1	2	8
Total medication adjustments, n (%)	11 (26)	20 (46)	10 (27)	7 (18)	3 (8)	12 (31)	21 (62)	20 (54)	45	59
Total participants with adjustments, n (%)	8 (19)	13 (30)	7 (19)	6 (15)	3 (8)	10 (26)	13 (38)	15 (41)	24 (56)	27 (61)

Data is presented as number of changes unless otherwise indicated. HIIT – high intensity interval training; MICT – moderate intensity continuous training; ACE – angiotensin-converting enzyme.

eTable 2. Serious adverse events

Event #	Group	Type	Severity	Related to Exercise	Remained in the study	Omitted from testing	Reason for the event
Stage 1 (Weeks 1-4)							
#1	MICT	Stroke	Hospitalisation	No	Yes	Week 4	Post-operative complication
#2	HIIT	Post-exercise hypotension	Medical emergency	Yes	Yes	No	Addition of diuretic medication
#3	HIIT	Pericarditis	Hospitalisation	No	No	All follow-up testing	Post-operative complication
#4	MICT	Atrial fibrillation	Hospitalisation	No	Yes	No	History of paroxysmal atrial fibrillation
Stage 2 (Weeks 5-12)							
#5	HIIT	Pericarditis	Hospitalisation	No	Yes	3 month	Post-operative complication
Stage 3 (Weeks 13-52)							
#6	HIIT	Third degree AV block, pacemaker insertion	Hospitalisation	No	No	6 month and 12 month	History of first degree AV block
#7	HIIT	Unstable angina, coronary stent	Hospitalisation	No	Yes	No	In-stent restenosis
#8	MICT	Unstable angina coronary stent	Hospitalisation	No	No	12 month	Residual CAD
#9	HIIT	NSTEMI, coronary stent	Hospitalisation	No	No	12 month	Residual CAD

SAEs are described as individual episodes.
HIIT – High intensity interval training; MICT – Moderate intensity continuous training; CAD – Coronary artery disease, AV – Atrioventricular, NSTEMI – Non-ST-elevation myocardial infarction.

eTable 3. Exercise intensity during stages 1 and 2

	Supervised training			Home-based training		
	Stage 1 (weeks 1-4)			Stage 2 (weeks 5-12)		
Measure of exercise intensity	**HIIT (n=43)**	**MICT (n=43)**	**p value**	**HIIT (n=37)**	**MICT (n=40)**	**p value**
Average training RPE	16.0 ± 1.1	12.4 ± 0.6	<0.001*	16.5 ± 1.2	12.4 ± 0.5	<0.001*
Peak training RPE	16.5 ± 1.1	12.7 ± 0.6	<0.001*	16.9 ± 1.2	12.5 ± 0.5	<0.001*
Average training $\%HR_{peak}$ (based on highest CPET)	87 ± 6	70 ± 8	<0.001*	88 ± 7	NR	---
Peak training $\%HR_{peak}$ (based on highest CPET)	90 ± 6	72 ± 8	<0.001*	89 ± 7	NR	---
Average training $\%HR_{peak}$ (based on baseline CPET)	91 ± 5	75 ± 9	<0.001*	93 ± 6	NR	---
Peak training $\%HR_{peak}$ (based on baseline CPET)	94 ± 5	76 ± 9	<0.001*	95 ± 9	NR	---

Values are presented as mean ± standard deviation unless otherwise stated. Symbol * denotes significant difference between groups.
HIIT – high intensity interval training; MICT – moderate intensity continuous training; RPE – rating of perceived exertion; n – number of participants; $\%HR_{peak}$ – percentage of peak heart rate; CPET – cardiopulmonary exercise test; NR – not recorded at this timepoint. $\%HR_{peak}$ was calculated from the CPET with highest HR_{peak} attained over the 12 months, unless the change in HR_{peak} was associated with adjustments to β-blockade.

eTable 4. Adherence to exercise training protocols

	Supervised training			Home-based training								
	4 weeks			3 months			6 months			12 months		
Outcome measure	**HIIT (n=44)**	**MICT (n=43)**	**p value**	**HIIT (n=37)**	**MICT (n=41)**	**p value**	**HIIT (n=37)**	**MICT (n=39)**	**p value**	**HIIT (n=34)**	**MICT (n=37)**	**p value**
Adherence to exercise training protocols, n (%)	39 (91)	39 (91)	1.000	25 (68)	30 (75)	0.614	21 (57)	15 (38)	0.107	18 (53)	15 (41)	0.346
• Adherence to attendance at exercise sessions, n (%)	43(100)	39 (91)	0.116	25 (68)	31 (78)	0.443	24 (65)	26 (67)	1.000	19 (56)	26 (70)	0.229
• Adherence to prescribed exercise intensity, n (%)	39 (91)	42 (98)	0.360	31 (84)	35 (88)	0.750	26 (70)	21 (54)	0.241	23 (68)	18 (49)	0.149
Total exercise sessions per week	3.3 ±1.0	4.1 ±1.6	**0.014***	2.8 ± 1.7	3.3 ± 1.8	0.255	3.5 ± 1.5	3.7 ± 1.6	0.643	3.1 ± 1.8	3.5 ± 2.1	0.495
Total exercise minutes per week	125 ± 59	200 ± 123	**0.001***	142 ± 114	193 ± 135	0.083	145 ± 89	174 ± 92	0.228	138 ± 112	173 ± 134	0.243

Classification of participants not training at the recommended exercise intensity		
Group	**6 months**	**12 months**
HIIT	Not training at recommended exercise intensity = 30% of participants • 8% performing interval training at a lower intensity (<RPE 15) • 8% performing a form of MICT instead of HIIT • 8% performing a form of MICT in combination with HIIT • 5% not performing any exercise	Not training at recommended exercise intensity = 32% of participants • 9% performing interval training at a lower intensity (<RPE 15) • 8% performing a form of MICT instead of HIIT • 3% performing a form of MICT in combination with HIIT • 12% not performing any exercise
MICT	Not training at recommended exercise intensity = 46% of participants • 28% performing continuous training at a higher intensity (≥RPE 15) • 5% performing a form of HIIT instead of MICT • 5% performing a form of HIIT in combination with MICT • 3% performing continuous training at a lower intensity (RPE<11) • 3% performing interval training at a moderate intensity (RPE 11-13) • 3% not performing any exercise	Not training at recommended exercise intensity = 51% of participants • 14% performing continuous training at a high intensity (≥RPE 15) • 3% performing a form of HIIT instead of MICT • 16% performing HIIT in combination with MICT • 5% performing continuous training at a lower intensity (<RPE 11) • 14% not performing any exercise

Values are presented as mean ± standard deviation unless otherwise stated. Symbol * denotes significant difference between groups.
HIIT – high intensity interval training; MICT – moderate intensity continuous training. Adherence to the exercise training protocol involves: ≥ 70% attendance at the recommended number of exercise sessions and whether the participant trained at the recommended exercise intensity prescription during the exercise sessions.

eTable 5. Per-protocol analyses

Outcome measure	n	Supervised training (Stage 1)				Group *Time Effect	n	Home-based training (Stage 3)				Effect	
		Baseline		Change in 4 weeks				Baseline		Change in 12 months		Time	Group *Time
		HIIT	MICT	HIIT	MICT			HIIT	MICT	HIIT	MICT		
CARDIORESPIRATORY FITNESS AND VENTILATORY EFFICIENCY													
Peak oxygen uptake (ml/kg/min)	78	28.4 ± 6.2	27.9 7.3	3.2* (2.1, 4.3)	1.1* (0.1, 2.2)	0.010	33	29.3 ± 6.6	26.0 ± 8.5	5.2* (3.3, 7.2)	2.2* (0.0, 4.3)	**<0.001**	**0.039**
Peak Oxygen uptake (mL/kgLBM/min)	78	41.9 ± 7.5	42.1 9.3	4.5* (2.9, 6.1)	1.0 (-0.6, 2.5)	**0.002**	33	42.1 ± 8.6	38.5 10.2	7.1* (4.3, 10.0)	2.0 (-1.2, 5.1)	**<0.001**	**0.019**
Peak oxygen uptake (L/min)	78	2.41 ± 0.62	2.40 ± 0.66	0.25* (0.16, 0.35)	0.09 (0.0, 0.18)	**0.017**	33	2.40 ± 0.67	2.01 ± 0.65	0.36* (0.22, 0.51)	0.09 (-0.07, 0.25)	**<0.001**	**0.015**
Peak respiratory exchange ratio	78	1.14 ± 0.09	1.14 ± 0.09	-0.02 (-0.05, 0.02)	-0.01 (-0.04,0.02)	0.782	33	1.17 ± 0.1	1.13 ± 0.1	-0.04 (-0.08, 0.01)	0.00 (-0.05, 0.05)	0.232	0.264
Peak heart rate (beats/min)	78	153 ± 17	147 ± 20	0 (-4, 4)	-2 (-5, 2)	0.556	33	155 ± 17	142 ± 18	3 (-5, 10)	11* (3, 19)	**0.017**	0.152
Peak oxygen pulse (mL/beat)	78	15.8 ± 3.9	16.2 ± 3.6	1.8* (1.1, 2.5)	0.8* (0.1, 1.5)	**0.047**	33	15.5 ± 3.7	14.1 ± 3.8	2.1* (1.1, 3.1)	-0.5 (-1.6, 0.6)	**0.029**	**0.001**
Maximal OUES	78	2.5 ± 0.8	2.4 ± 0.6	0.3* (0.1, 0.4)	0.2* (0.0, 0.4)	0.584	33	2.6 ± 0.8	2.1 ± 0.6	0.3* (0.1, 0.5)	0.1 (-0.2, 0.3)	**0.032**	0.111
CARDIOVASCULAR RISK FACTORS													
Body mass (kg)	78	84 ± 14	86 ± 15	-1* (-1, 0)	-1* (-1, 0)	0.730	33	81 ± 13	77 ± 12	-1.8* (-3.2, -0.4)	-2.5* (-4.0, -0.9)	**<0.001**	0.524
Body mass index (kg/m)	78	27.8 ± 4.1	28.1 ± 3.9	-0.1 (-0.4, 0.2)	-0.3* (-0.6, 0.0)	0.304	33	27.1 ± 3.0	26.1 ± 3.2	-0.6* (-1.2, -0.1)	-1.2* (-1.8, -0.6)	**<0.001**	0.193
Waist circumference (cm)	78	99.6 ± 12.5	98.5 ± 11.1	-2.0* (-3.1, -1.0)	-1.6* (-2.6, -0.5)	0.529	33	96.4 ± 12.3	92.9 ± 11.4	-3.7* (-5.9, 1.5)	-4.8* (-7.3, 2.3)	**<0.001**	0.512
Waist to Hip Ratio	78	0.96 ± 0.08	0.94 ± 0.07	-0.01* (-0.02, 0.00)	-0.01* (-0.03, 0.00)	0.930	33	0.93 ± 0.10	0.92 ± 0.07	-0.02* (-0.04, -0.01)	-0.03* (-0.05, -0.02)	**<0.001**	0.401
Waist to Height Ratio	78	0.57 ± 0.07	0.56 ± 0.06	-0.01* (-0.02, 0.01)	-0.01* (-0.03, 0.00)	0.670	33	0.56 ± 0.06	0.54 ± 0.06	-0.02* (-0.03, -0.01)	-0.03* (-0.04, -0.01	**<0.001**	0.534
Lean body mass (kg)	78	57.0 ± 8.9	56.8 ± 9.6	0.1 (-0.3, 0.6)	0.5* (0.1, 1.0)	0.176	33	56.7 ± 9.7	52.1 ± 9.3	-0.5 (-1.3, 0.3)	-0.6 (-1.5, 0.3)	**0.067**	0.880
Visceral adipose tissue DEXA (cm_2)	78	193 ± 78	193 ± 73	-10* (-15, -5)	-10* (-15, -5)	0.819	33	166 ± 75	160 ± 64	-14* (-28, -1)	-18* (-33, -4)	**0.002**	0.697

Total cholesterol (mg/dL)	78	143 ± 27	139 ± 31	-4 (-12, 4)	4 (-4, 8)	0.140	33	147 ± 35	143 ± 31	4 (-12, 15)	4 (-8, 19)	0.390	0.697
LDL cholesterol (mg/dL)	78	73 ± 23	73 ± 23	-4 (-12, 4)	-4 (-4, 8)	0.154	33	73 ± 31	69 ± 23	-4 (-15, 4)	0.0 (-12, 12)	0.630	0.385
HDL cholesterol (mg/dL)	78	50 ± 12	50 ± 15	0 (0, 4)	0 (0, 4)	0.807	33	50 ± 12	54 ± 19	4* (0, 8)	4* (0, 8)	**0.002**	0.946
Triglycerides (mmol/L)	78	115 ± 142	97 ± 35	-18 (-35, 9)	0 (-27, 18)	0.500	33	97 ± 27	97 ± 44	0 (-27, 18)	0 (-27, 27)	0.986	0.844
Fasting glucose (mg/dL)	78	106 ± 32	108 ± 22	-4 (-13, 4)	-2 (-7, 9)	0.366	33	103 ± 9	110 ± 25	-2 (-7, 2)	2 (-4, 7)	0.850	0.273
Insulin Resistance (HOMA-IR)	78	2.8 ± 2.2	2.4 ± 1.9	-0.2 (-0.8, 0.3)	-0.1 (-0.7, 0.4)	0.795	33	2.3 ± 1.7	2.4 ± 2.2	-0.5 (-1.2, 0.2)	0.0 (-0.7, 0.8)	0.339	0.279
Resting heart rate (beats/min)	78	55 ± 9	55 ± 8	-2* (-4, 0)	-1 (-3, 1)	0.203	33	55 ± 9	52 ± 6	-3 (-5, 0)	2 (-1, 5)	0.630	**0.035**
Peripheral, systolic blood pressure (mmHg)	78	127 ± 16	129 ± 14	3 (-1, 6)	-4* (-8, -1)	**0.011**	33	131 ± 19	129 ± 16	2 (-6, 10)	-3 (-12, 5)	0.783	0.353
Peripheral, diastolic blood pressure (mmHg)	78	74 ± 10	74 ± 9	2 (0, 4)	-2 (-4, 0)	**0.012**	33	76 ± 11	70 ± 6	0 (-4, 4)	0 (-4, 4)	0.945	0.977
QUALITY OF LIFE AND EXERCISE ENJOYMENT													
McNew – Global	78	5.9 ± 0.8	6.0 ± 0.6	0.5* (0.4, 0.7)	0.4* (0.2, 0.5)	0.164	33	6.0 ± 0.7	6.0 ± 0.6	0.5* (0.2, 0.8)	0.4* (0.1, 0.7)	**<0.001**	0.615
Exercise enjoyment (%)	77	74 ± 18	80 ± 14	2 (-3, 8)	1 (-4, 7)	0.811	33	77 ± 14	83 ± 10	1 (-8, 9)	-8 (-17, 1)	0.229	0.167

Per-protocol analysis includes only participants meeting the criteria for adherence to the exercise protocol. The adherence criteria involves ≥ 70% attendance at the recommended number of exercise sessions and training at the prescribed exercise intensity prescription during the exercise sessions. Baseline data results presented as mean ± standard deviation. Follow-up data results presented as mean change (95% confidence interval). P values are provided for group and time interaction effects after 4 weeks and 12 months and for time effects after 12 months. The symbol* denotes significant difference from baseline. HIIT - high intensity interval training; MICT – moderate intensity continuous training; ml.kgLBM.min-1 – normalised for lean body mass; OUES – oxygen uptake efficiency slope; DEXA – dual-energy x-ray absorptiometry; LDL – low-density lipoprotein; HDL – high-density lipoprotein; HOMA-IR – homeostatic model assessment of insulin resistance; MVPA – moderate to vigorous physical activity. SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; LDL cholesterol to millimoles per liter, multiply by 0.0259; HDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; fasting glucose to millimoles per liter, multiply by 0.0555.

eTable 6. Participant feasibility

	4 weeks			3 months			6 months			12 months		
Feasibility question	**HIIT (n=43)**	**MICT (n=43)**	**p value**	**HIIT (n=37)**	**MICT (n=40)**	**p value**	**HIIT (n=37)**	**MICT (n=39)**	**p value**	**HIIT (n=34)**	**MICT (n=37)**	**p value**
Intention to continue with exercise protocol												
Yes – willing to continue this exercise protocol, n (%)	42 (98)	42 (98)	1.000	37 (100)	40 (100)	1.000	37 (100)	39 (100)	1.000	31 (91)	34 (92)	1.000
No – not willing to continue this exercise protocol, n (%)	1 (2)	1 (2)	1.000	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000	3 (9)	3 (8)	1.000
Performing exercise protocol (based on 7-point likert scale)												
Confidence in performing exercise protocol	6.6 (6.4, 6.8)	6.4 (6.1, 6.7)	0.501	6.6 (6.4, 6.8)	6.4 (6.1, 6.7)	0.312	6.1 (5.7, 6.5)	6.3 (5.9, 6.6)	0.363	6.2 (5.7, 6.6)	6.0 (5.4, 6.6)	0.934
Ability to independently manage exercise intensity	6.5 (6.3, 6.7)	6.1 (5.8, 6.4)	**0.040**	6.6 (6.4, 6.8)	6.2 (5.9, 6.5)	0.177	6.2 (6.0, 6.5)	6.1 (5.7, 6.5)	0.955	6.2 (5.8, 6.7)	5.8 (5.3, 6.3)	0.132
Enjoyment of exercise protocol	5.5 (5.0, 5.9)	5.4 (5.0, 5.9)	0.914	5.6 (5.2, 6.1)	5.5 (5.0, 6.0)	0.882	5.2 (4.8, 5.7)	5.3 (4.8, 5.7)	0.957	5.4 (4.9, 6.0)	5.5 (4.9, 6.0)	0.744
Ease of understanding instructions for exercise protocol	6.6 (6.4, 6.8)	6.3 (6.0, 6.6)	0.286	6.9 (6.8, 7.0)	6.6 (6.3, 6.8)	**0.010**	NR	NR	NR	NR	NR	NR
Completion of exercise protocol												
How often was the participant unable to complete their exercise protocol, n (%)												
Never	24 (56)	18 (42)	0.281	14 (39)	14 (35)	0.817	13 (35)	15 (39)	0.815	9 (27)	9 (24)	1.000
Occasionally	18 (40)	22 (51)	0.386	20 (54)	18 (45)	0.497	20 (54)	22 (56)	1.000	20 (59)	23 (62)	0.812
Frequently	2 (5)	3 (7)	1.000	3 (8)	8 (20)	0.196	4 (11)	2 (5)	0.425	5 (15)	5 (14)	1.000
Reasons for being unable to complete their protocol, n												
Fatigue	1	2		2	2		2	3		4	3	
Unwell/illness	6	8		3	6		5	4		6	7	
Injury	3	5		8	8		5	4		7	6	
Low motivation	1	2		3	6		1	4		4	5	
Work/other commitments	4	8		5	7		8	4		5	6	
Travel	1	0		1	4		1	5		2	3	
Weather	0	0		3	1		3	2		1	1	

Feasibility question	4 weeks			3 months			6 months			12 months		
	HIIT (n=43)	MICT (n=43)	p value	HIIT (n=37)	MICT (n=40)	p value	HIIT (n=37)	MICT (n=39)	p value	HIIT (n=34)	MICT (n=37)	p value
Unpleasant effects or symptoms from exercise												
How often did the participant experience unpleasant effects or symptoms from their exercise protocol, n (%)												
Never	30 (71)	34 (79)	0.459	27 (73)	27 (68)	0.628	30 (81)	27 (71)	0.419	21 (62)	28 (76)	0.304
Occasionally	11 (26)	9 (21)	0.616	10 (27)	13 (33)	0.628	6 (16)	9 (24)	0.565	12 (35)	8 (22)	0.291
Frequently	1 (2)	0 (0)	0.494	0 (0)	0 (0)	1.000	1 (3)	2 (5)	1.000	1 (3)	1 (3)	1.000
Unpleasant effects or symptoms reported, n												
Chest pain/angina	1	2		2	2		2	1		1	3	
Light-headedness	3	2		1	1		0	2		0	0	
Palpitations / suspected arrhythmia	1	0		1	1		0	0		2	0	
Shortness of breath	2	1		1	1		0	0		1	0	
Fatigue	1	1		2	0		1	2		1	1	
Joint pain / fatigue	3	1		1	3		1	3		3	0	
Muscle pain / fatigue	1	4		1	2		1	1		1	1	
Other (e.g. foot pain, dehydration)	2	0		0	1		0	1		0	1	

Values are presented as mean (95% confidence interval) unless otherwise stated. Significance is ≤ 0.05.
HIIT – high intensity interval training; MICT – moderate intensity continuous training; n – number of participants; NR – not recorded at this time-point.

eTable 7. Sensitivity analyses

Outcome measure	n	Supervised training (Stage 1)				Group *Time Effect	Home-based training (Stages 2 and 3)						Effect	
		Baseline		Change in 4 weeks			Change in 3 months		Change in 6 months		Change in 12 months		Time	Group *Time
		HIIT	MICT	HIIT	MICT		HIIT	MICT	HIIT	MICT	HIIT	MICT		
CARDIORESPIRATORY FITNESS AND EFFICIENCY – medications included as covariates †														
Peak heart rate (beats/min)	93	151 ± 17	150 ± 20	1 (-2, 4)	-2 (-6, 1)	0.251	3 (-3, 9)	2 (-3, 8)	2 (-4, 8)	2 (-4, 8)	2 (-4, 8)	6* (0, 12)	**0.003**	0.174
Peak oxygen pulse (mL/beat)	93	15.5 ± 3.8	15.9 ± 4.0	1.6* (0.9, 2.2)	0.9* (0.2, 1.6)	0.141	0.8 (-0.3, 1.9)	0.7 (-0.3, 1.8)	1.1 (0.0, 2.2)	0.2 (-0.8, 1.3)	1.1 (-0.1, 2.2)	0.1 (-1.0, 1.2)	**<0.001**	0.282
CARDIORESPIRATORY FITNESS AND EFFICIENCY - excluding medication adjustments #														
Peak heart rate (beats/min)	83 / 78	151 ± 17	151 ± 20	1 (-3, 4)	-1 (-5, 3)	0.491	1 (-5, 7)	3 (-3, 9)	1 (-5, 7)	1 (-5, 7)	1 (-5, 7)	5 (-1, 11)	0.114	0.281
Peak oxygen pulse (mL/beat)	83 / 78	15.6 ± 3.8	15.9 ± 4.1	1.6* (0.8, 2.3)	0.9* (0.1, 1.6)	0.181	0.9 (-0.3, 2.2)	1.0 (-0.2, 2.2)	1.0 (-0.2, 2.2)	0.6 (-0.6, 1.8)	0.8 (-0.5, 2.1)	0.3 (-0.9, 1.5)	**<0.001**	0.594
CARDIOVASCULAR RISK FACTORS – medications included as covariates †														
Total cholesterol (mg/dL)	93	147 ± 31	147 ± 31	-4 (-12, 0)	-4 (-8, 4)	0.627	-4 (-12, 8)	0 (-8, 8)	-4 (-12, 4)	0 (-8, 12)	0 (-8, 12)	12* (4, 23)	**0.002**	0.141
LDL cholesterol (mg/dL)	93	77 ± 27	73 ± 23	-4 (-12, 0)	0 (-8, 4)	0.474	-4 (-12, 8)	0 (-8, 8)	-4 (-12, 4)	0 (-8, 8)	-4 (-12, 4)	8 (-4, 15)	0.170	0.170
HDL cholesterol (mg/dL)	93	50 ± 12	50 ± 15	0 (0, 4)	0 (0, 4)	0.808	4* (0, 8)	0 (0, 4)	4 (0, 4)	4 (0, 4)	4* (0, 8)	4* (4, 8)	**<0.001**	0.423
Triglycerides (mg/dL)	93	124 ± 133	106 ± 53	-18 (-35, 9)	-9 (-27, 9)	0.575	-18 (-35, 9)	-9 (-29, 9)	-9 (-35, 9)	0 (-18, 18)	-9 (-35, 18)	9 (-9, 35)	0.078	0.592
Resting heart rate (beats/min)	93	57 ± 10	57 ± 8	-3* (-5, -1)	-1 (-3, 0)	0.192	-3* (-6, 0)	-2 (-5, 1)	-4* (-7, -2)	-1 (-4, 2)	-4* (-7, -1)	-3 (-5, 0)	**<0.001**	0.205
Peripheral, systolic blood pressure (mmHg)	93	128 ± 15	130 ± 14	2 (-1, 5)	-4* (-7, 0)	**0.019**	1 (-5, 6)	-4 (-9, 2)	1 (-4, 7)	-4 (-9, 2)	2 (-3, 8)	+1 (-3, 6)	0.223	0.093
Peripheral, diastolic blood pressure (mmHg)	93	75 ± 10	74 ± 9	1 (-1, 3)	-2* (-4, 0)	**0.029**	0 (-3, 3)	-2 (-4, 1)	-1 (-4, 2)	-2 (-5, 1)	0 (-3, 3)	1 (-2, 4)	0.081	0.075
CARDIOVASCULAR RISK FACTORS - excluding medication adjustments #														
Total cholesterol (mg/dL)	88 / 76	147 ± 31	147 ± 31	-4 (-12, 0)	-4 (-8, 4)	0.931	-4 (-12, 8)	-4 (-12, 8)	-4 (-12, 8)	0 (-12, 8)	4 (-8, 12)	8 (-4, 19)	**0.001**	0.863
LDL cholesterol (mg/dL)	88 / 76	77 ± 27	73 ± 23	-4 (-8, 0)	-4 (-8, 4)	0.744	-4 (-12, 4)	-4 (-12, 4)	-4 (-12, 4)	0 (-8, 8)	0 (-12, 8)	0 (-8, 12)	0.124	0.922
HDL cholesterol (mg/dL)	88 / 76	50 ± 12	50 ± 15	0 (0, 4)	0 (0, 4)	0.889	4 (0, 4)	0 (0, 4)	4 (0, 4)	4 (0, 8)	4* (0, 8)	4* (0, 8)	**<0.001**	0.777

Triglycerides (mg/dL)	88 / 76	124 ± 133	106 ± 53	-9 (-35, 9)	-9 (-27, 18)	0.667	-18 (-35, 9)	-9 (-27, 18)	-9 (-35, 9)	0 (-27, 18)	-9 (-35, 9)	9 (-18, 27)	0.265	0.695
Resting heart rate (beats/min)	83 / 78	57 ± 10	58 ± 8	-3* (-4, -1)	-1 (-3, 0)	0.734	-3* (-6, -1)	-3 (-5, 0)	-5* (-8, -2)	-2 (-5, 0)	-3* (-6, 0)	-3 (-5, 0)	**<0.001**	0.312
Peripheral, systolic blood pressure (mmHg)	76 / 64	128 ± 13	129 ± 13	2 (-2, 6)	-4* (-8, 0)	**0.025**	0 (-7, 7)	-5 (-11, 1)	2 (-5, 8)	-5 (-11, 1)	3 (-4, 10)	-1 (-7, 5)	0.321	0.230
Peripheral, diastolic blood pressure (mmHg)	76 / 64	75 ± 8	74 ± 9	1 (-1, 3)	-1 (-3, 1)	0.068	0 (-4, 3)	-1 (-4, 2)	-1 (-4, 3)	-2 (-5, 1)	1 (-3, 4)	1 (-1, 5)	0.210	0.272
CARDIOVASCULAR RISK FACTORS – hypertension subgroup														
Peripheral, systolic blood pressure (mmHg)	52	141 ± 10	138 ± 9	-5* (-10, -1)	-6* (-10, -2)	0.734	-4 (-12, 4)	-7 (-13, 0)	-6 (-14, 2)	-8* (-14, -1)	-8 (-16, 0)	-3 (-10, 3)	**0.001**	0.360
Peripheral, diastolic blood pressure (mmHg)	52	82 ± 7	78 ±10	-2 (-5, 0)	-2 (-4, 0)	0.953	-2 (-7, 2)	-2 (-6, 1)	-7* (-11, -2)	-4 (-9, 0)	-5 (-9, 0)	-1 (-4, 3)	**<0.001**	0.113

Baseline data results presented as mean ± standard deviation. Follow-up data results presented as mean change (95% confidence interval). P values are provided for group and time interaction effects after 4 weeks and 12 months and for time effects after 12 months. The symbol* denotes significant difference from baseline.

HIIT - high intensity interval training; MICT – moderate intensity continuous training; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

Sensitivity analyses were performed to account for medication adjustments, either ŧincluding medications as covariates, #excluding participants with adjustments. For cardiorespiratory fitness variables involving heart rate, β-blocker adjustments were accounted for due to their effect on heart rate regulation and response. For cholesterol variables, statin and/or Ezetimbe adjustments were accounted for due to their effect on cholesterol metabolism. For blood pressure variables, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers, and diuretics adjustments were accounted for due to their use in management of blood pressure.

Sensitivity analyses were also performed for a hypertension subgroup of participants. Hypertension was classified by resting systolic blood pressure > 130mmHg for at least two measurements.

SI conversion factors: To convert total cholesterol to millimoles per liter, multiply by 0.0259; LDL cholesterol to millimoles per liter, multiply by 0.0259; HDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; fasting glucose to millimoles per liter, multiply by 0.0555.

eTable 8. Habitual physical activity and dietary intake

Outcome Measures	n	Supervised Training (Stage 1)				Effect	Home-based training (Stages 2 and 3)						Effect	
		Baseline		Change in 4 weeks		Time* Group	Change in 3 months		Change in 6 months		Change in 12 months		Time	Time* Group
		HIIT	MICT	HIIT	MICT		HIIT	MICT	HIIT	MICT	HIIT	MICT		
HABITUAL PHYSICAL ACTVITY														
Average daily MVPA (minutes)	84	26 ± 19	31 ± 23	6* (0, 12)	0 (-6, 7)	0.193	4 (-6, 14)	4 (-5, 14)	6 (-3, 16)	-2 (-12, 8)	9 (-2, 20)	2 (-8, 13)	0.262	0.232
Average daily acceleration (mg)	83	18.6 ± 8.2	18.4 ± 7.5	2.6* (1.2, 4.1)	1.4 (-0.1, 3.0)	0.262	2.9* (0.4, 5.4)	2.2 (-0.2, 4.7)	2.8* (0.3, 5.2)	1.7 (-0.9, 4.3)	4.0* (1.2, 6.7)	2.0 (-0.6, 4.7)	**<0.001**	0.559
Minimum acceleration for most active 30 min (mg)	83	130 ± 51	133 ± 45	16* (5, 26)	1 (-9, 13)	0.067	9 (-15, 34)	14 (-9, 38)	10 (-15, 34)	11 (-14, 36)	24 (-3, 51)	24 (-2, 50)	**0.011**	0.409
HABITUAL DIETARY INTAKE														
Energy intake (MJ)	91	8.6 ± 2.2	8.5 ± 2.7	-0.2 (-0.8, 0.5)	-0.4 (-1.1, 0.2)	0.589	-0.2 (-1.1, 0.8)	-0.1 (-1.0, 0.8)	0.2 (-0.8, 1.1)	-0.1 (-1.1, 0.8)	0.1 (-0.8, 1.1)	0 (-0.9, 0.9)	0.443	0.913
Protein (g)	91	94 ± 26	94 ± 30	2 (-8, 12)	-1 (-11, 9)	0.714	5 (-9, 19)	-4 (-18, 10)	9 (-5, 23)	-3 (-17, 10)	5 (-9, 19)	4 (-10, 18)	0.697	0.320
Fat (g)	91	78 ± 30	82 ± 33	-3 (-12, 7)	-9* (-19, 0)	0.334	3 (-10, 16)	-3 (-16, 10)	3 (-10, 16)	-9 (-22, 4)	6 (-8, 19)	-3 (-16, 10)	0.120	0.439
Carbohydrate (g)	91	199 ± 67	197 ± 76	-14 (-32, 5)	-10 (-28, 8)	0.795	-14 (-42, 15)	-6 (-35, 22)	5 (-24, 34)	-5 (-34, 23)	9 (-21, 38)	-13 (-41, 16)	0.275	0.295

Baseline results data presented as mean ± standard deviation. Follow-up data presented as mean change (95% confidence interval). P values are provided for group and time interaction effects after 4 weeks and 12 months and for time effects after 12 months. The symbol* denotes significant difference from baseline. HIIT - high intensity interval training; MICT – moderate intensity continuous training; MVPA – moderate to vigorous physical activity