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FULL RESEARCH PAPER
Cardiac rehabilitation

High-intensity interval training in cardiac rehabilitation: a multi-centre randomized controlled trial

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Background There is a lack of international consensus regarding the prescription of high-intensity interval training (HIIT) for people with coronary artery disease (CAD) attending cardiac rehabilitation (CR).

Aims To assess the clinical effectiveness and safety of low-volume HIIT compared with moderate-intensity steady-state (MISS) exercise training for people with CAD.

Methods and results We conducted a multi-centre RCT, recruiting 382 patients from 6 outpatient CR centres. Participants were randomized to twice-weekly HIIT ($n = 187$) or MISS ($n = 195$) for 8 weeks. HIIT consisted of 10 × 1 min intervals of vigorous exercise (>85% maximum capacity) interspersed with 1 min periods of recovery. MISS was 20–40 min of moderate-intensity continuous exercise (60–80% maximum capacity). The primary outcome was the change in cardiorespiratory fitness [peak oxygen uptake ($VO_{2\ peak}$)] at 8 week follow-up. Secondary outcomes included cardiovascular disease risk markers, cardiac structure and function, adverse events, and health-related quality of life. At 8 weeks, $VO_{2\ peak}$ improved more with HIIT (2.37 $mL.kg^{-1}.min^{-1}$; SD, 3.11) compared with MISS (1.32 $mL.kg^{-1}.min^{-1}$; SD, 2.66). After adjusting for age, sex, and study site, the difference between arms was 1.04 $mL.kg^{-1}.min^{-1}$ (95% CI, 0.38 to 1.69; $P = 0.002$). Only one serious adverse event was possibly related to HIIT.

Conclusions In stable CAD, low-volume HIIT improved cardiorespiratory fitness more than MISS by a clinically meaningful margin. Low-volume HIIT is a safe, well-tolerated, and clinically effective intervention that produces short-term improvement in cardiorespiratory fitness. It should be considered by all CR programmes as an adjunct or alternative to MISS.

Trial registration ClinicalTrials.gov: NCT02784873. https://clinicaltrials.gov/ct2/show/NCT02784873.

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Lay summary Cardiac rehabilitation exercise training can improve cardiorespiratory fitness and quality of life for people with coronary artery disease, but sometimes, it is not effective. The intensity of the exercise training may be important. We conducted a randomized controlled trial to test if moderate-intensity exercise or high-intensity exercise was better.

- High-intensity interval training was more effective than moderate-intensity exercise training for improving cardiorespiratory fitness in people with coronary artery disease attending cardiac rehabilitation.
- High-intensity interval training was safe and well tolerated.

Keywords Cardiac rehabilitation • Exercise training • High-intensity interval training • Coronary artery disease • Cardiorespiratory fitness • National Health Service

Introduction

Exercise training is a central pillar of multidisciplinary rehabilitation for people with coronary artery disease (CAD). As an integral component of contemporary secondary prevention models, exercise training can contribute to improved physical and mental health but, in its current form, may not reduce all-cause or cardiovascular mortality.[1,2] With the intention of improving quality of life, maintaining functional independence, and as a proxy for survival,[3–5] cardiac rehabilitation (CR) exercise training guidelines explicitly target improvements in cardiorespiratory fitness [peak oxygen uptake ($VO_{2\ peak}$)], an important clinical outcome. However, current guidelines for CAD vary considerably, most notably in terms of exercise intensity.[6] On the basis that greater improvements in cardiorespiratory fitness are likely to be achieved,[7] guidelines from some countries in North America and Europe recommend higher-intensity exercise whilst others, including the UK, do not.[8]

Progression from moderate-intensity (<80% $VO_{2\ peak}$) interval training towards continuous moderate-intensity steady-state (MISS) exercise is currently considered best practice for CR in many countries.[6] However, studies have shown this to be insufficient to meaningfully increase cardiorespiratory fitness.[9,10] High-intensity interval training (HIIT), involving repeated bursts of vigorous exercise (>85% $VO_{2\ peak}$) interspersed with periods of recovery, has been proposed as a more effective alternative.[11] However, studies using a 4 min high-intensity interval protocol in cardiac patients showed no additional benefit with HIIT.[12,13] This was likely due to participants not achieving the prescribed intensity for the duration of the 4 min high-intensity intervals.[12,13] In contrast, small proof-of-concept studies have shown low-volume HIIT (1 min high-intensity intervals interspersed with 1 min periods of recovery) to be effective and well tolerated.[14,15] The safety and effectiveness of low-volume HIIT protocols have not been tested in a definitive clinical trial.

Against the backdrop of an equivocal evidence base and the need to assess the safety and effectiveness of low-volume HIIT in routine CR, we conducted a pragmatic, multi-centre, randomized controlled trial to evaluate the effectiveness of two CR exercise prescriptions: (i) low-volume HIIT and (ii) MISS training.[16] The primary objective was to evaluate changes in cardiorespiratory fitness ($VO_{2\ peak}$). Secondary objectives included assessment of adverse events, fidelity, tolerability, cardiovascular disease risk markers, cardiac structure and function, and health-related quality of life (HRQoL).

Methods

Trial design and setting

We conducted a pragmatic, parallel-group, assessor-blind, RCT to test the effectiveness of low-volume HIIT compared with MISS in six UK CR programmes (July 2016 to March 2020). The trial protocol was published previously,[16] and the protocol v1.0, dated 1 February 2016, was approved by the NHS Health Research Authority, East Midlands—Leicester South Research Ethics Committee—on 4 March 2016 (16/EM/0079). The trial was prospectively registered with ClinicalTrials.gov: NCT02784873 and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline.[17]

Participants and procedures

Patients referred for CR with acute myocardial infarction (MI), coronary artery bypass graft (CABG) surgery, angiographically documented CAD, and/or elective percutaneous coronary intervention (PCI) were eligible. Participants aged 18–80 years must have been successfully revascularized (where indicated), have left ventricular ejection fraction > 35%, and be clinically stable (symptoms and medication) for more than 2 weeks. Exclusions were exercise-induced ischaemia or haemodynamic compromise, NYHA class III–IV symptoms, and significant limiting comorbidities, e.g. musculoskeletal, that would prevent full participation.

Cardiac rehabilitation

Participants attended CR twice-weekly for 8 weeks, performing either HIIT or MISS for the cardiovascular component of their exercise programme. In accordance with UK standards, a 10–15 min progressive cardiovascular and mobility warm-up consisting of walking and cycle ergometry[18] and a muscular strength and endurance training programme were completed in both trial arms, whilst participation in a group education programme and home-based exercise was recommended. Further to completion of the 8-week HIIT or MISS intervention, participants were advised to continue with independent exercise and physical activity until the 12 month follow-up timepoint but were not provided with any structured sessions.

Low-volume high-intensity interval training (HIIT)

Low-volume HIIT consisted of 1 min intervals on a cycle ergometer (Wattbike Trainer, Wattbike, Nottingham, UK); 10 intervals at high intensity [85–90% peak power output (PPO) achieved during cardiopulmonary exercise test (CPET); > 85% HR_{max}] interspersed with 10 intervals at low intensity (20–25% PPO). Changes between low and high intensity were achieved by altering cadence. Once participants were able to complete all 10 × 1 min intervals, intensity was increased, as tolerated, every other week if rating of perceived exertion (RPE) was <17 during the last two high-intensity intervals.

Moderate-intensity steady-state (MISS) training

As per existing UK clinical practice, exercise was conducted within the framework provided by the Association for Chartered Physiotherapists in Cardiac Rehabilitation (ACPICR) standards.[18] Cardiovascular exercise initially consisted of moderate-intensity interval training progressing towards 20–40 min continuous exercise at 40–70% heart rate reserve (HRR, equivalent to 60–80% maximal exercise capacity). The initial session duration was based on participants' previous and current physical activity levels and CPET

performance. Duration and workload were adjusted, as tolerated, within the above parameters.

Outcome measures

Outcomes were assessed at baseline, 8 weeks, and 12 months. The primary outcome was the change in $VO_{2\ peak}$ ($mL.kg^{-1}.min^{-1}$) between baseline and 8 weeks measured during CPET using a standard bicycle ramp protocol (15, 20, or 25 $W.min^{-1}$) in accordance with guidelines.[19] Participants were encouraged to maintain a cadence of 70 rpm until symptom limited volitional fatigue. Breath-by-breath expired gas analysis, ECG, and blood pressure were monitored. Criteria for a good participant effort included peak respiratory exchange ratio (RER) > 1.10, peak HR ≥ 85% predicted, and RPE ≥ 18.[20] As a non-effort-dependent measure of functional capacity, oxygen uptake at the ventilatory anaerobic threshold ($VO_{2\ AT}$) was determined via the V-slope method and confirmed with ventilatory equivalents.[20] $VO_{2\ AT}$ was determined automatically by computer software and overread and adjusted independently by an operator blinded to group allocation and the timepoint at which the test was conducted.

Secondary outcomes included clinical examination (e.g. resting heart rate, blood pressure, medical history, and cardiovascular risk factor assessment) and HRQoL with the five-item EuroQoL EQ-5D-5L.[21] The generic EQ-5D-5L produces a health utility score (1 = a state equivalent to full health; 0 = a state equivalent to being dead) and a self-rated health score via a visual analogue scale (100 = best health; 0 = worst health). Furthermore, to evaluate biochemical cardiovascular disease risk markers, whole blood samples were obtained via standard venipuncture techniques, allowed to clot, and then centrifuged at 4000 rpm for 10 min prior to serum being aliquoted and stored frozen at −80°C at a single centralized laboratory. Samples were analysed for creatinine, high-sensitivity C-reactive protein (hs-CRP), and full lipid profile in a single batch at the end of data collection. The estimated glomerular filtration rate (eGFR) was calculated in accordance with the National Institute for Health and Care Excellence (NICE) recommendations.[22] Transthoracic echocardiography to assess left ventricular structure and function was performed at baseline and 8 weeks as per existing guidelines[23,24] but not at 12 months due to logistical challenges.

Compliance and adherence to exercise training was determined by recording the number of sessions attended. Intervention fidelity was rigorously assessed by comparing the mean HR and RPE achieved during single sessions in weeks two, four, six, and eight. Subsequently, the mean of these sessions was calculated for each participant and for each trial arm as a whole. To determine tolerability, dropout was documented, along with a reason, where voluntarily provided. To assess safety, the nature, severity, and expectedness (defined a priori) of adverse events, in addition to the potential relatedness (unrelated, unlikely, possibly, probably, and definitely) to the interventions, were determined by the local principal investigator, ratified by the chief investigator, and recorded in line with the international principles of Good Clinical Practice (GCP).[25] By convention, serious adverse events were classified as any untoward medical occurrence that resulted in death, was immediately life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity.

Sample size

A 1.5 $mL.kg^{-1}.min^{-1}$ larger improvement of the primary outcome measure, $VO_{2\ peak}$, in the HIIT arm compared with the MISS arm was the target difference. Assuming a standard deviation (SD) of 4.5 $mL.kg^{-1}.min^{-1}$,[12] a sample size of 191 participants in each arm was sufficient to detect this difference with 90% power and a significance level of 5%. A conservative dropout of ∼25% yielded a recruitment target of 510 patients (255 per arm). After 36 months, it was determined that the recruitment target could not be achieved within the planned time frame but that dropout was lower than expected (∼15%). Accordingly, a revised target of 382 participants was set, of which data from 324 were required for the primary outcome to retain 85% power.

Randomization and allocation concealment

Participants were randomly allocated on a 1 : 1 basis up to 8 weeks of HIIT or MISS. The random allocation process was prepared by the trial statistician using a random number generator and implemented by a central telephone registration and randomization service at the University of Warwick Clinical Trials Unit. Randomization was stratified by site using random permuted blocks. To ensure allocation concealment, researchers requested randomization only after completion of all baseline assessments. Trial interventions were delivered by clinical CR staff (clinical exercise physiologists and physiotherapists). Data were anonymously entered into a secure, web-based application [Research Electronic Data Capture (REDCap)].[26]

Statistical analysis

Primary analyses were conducted on an 'intention to treat' basis, i.e. according to the arm that the participant was originally allocated to, irrespective of their adherence. Continuous data were summarized with mean and SD or median and interquartile range (IQR), and categorical data were summarized with frequency count and percentage. A positive change from baseline to 8 week or 12 month follow-up indicated improvement from baseline. A positive difference in the mean change between treatment arms indicated HIIT to be superior to MISS. Primary (change of $VO_{2\ peak}$ from baseline to 8 week follow-up) and secondary outcomes were compared between the HIIT and MISS arms using a generalized linear model where the outcome was changed from baseline to follow-up. Treatment effects are presented as adjusted and unadjusted between group differences. As pre-specified,[16] age (continuous), sex (categorical), and study site (categorical) were used in the adjusted generalized linear model.

A multiple imputation sensitivity analysis was conducted imputing the primary outcome and covariates in the model conditional on randomized treatment group. The Markov chain Monte Carlo (MCMC) procedure was used with 50 imputations and 100 burn-in iterations.

A per-protocol analysis estimated the treatment effect in the subgroup of participants in the HIIT and MISS arms who complied with the treatment protocol (see Supplementary material online, *Table S1*). The same analysis model as for the primary outcome analysis was used for imputation and per-protocol analyses. All *P*-values are two sided unless otherwise stated, and analyses were conducted using R (4.0.3).[27]

To supplement the intention to treat analysis of the primary outcome, we also completed a responder analysis. To do this and to account for differences in response due to measurement error and random within-subject variation,[28] we compared the intervention response SD (SD_{IR}) with a pre-selected MCID (1.0 mL/kg/min).[29] As the SD_{IR} was greater than the MCID in both the HIIT and MISS groups, we then calculated the probability that the true individual responses were greater than the MCID for each individual and categorized responses as either most unlikely (<5% chance), very unlikely (5–24% chance), possibly (25–74% chance), likely (75–94% chance), or very likely (95–100% chance) using the open-access software developed by Hopkins.[30] Positive responders were classified as those individuals who exceeded the 75% probability that their individual change in VO_{2peak} was greater than the MCID after adjusting for the typical error (TE) of measurement.[31] TE was calculated using VO_{2peak} data from 37 similarly aged cardiac patients assessed before and after a 10 week control period (i.e. non-exercise) (see Supplementary material online, *Table S2*).

Results

Between 1 September 2016 and 13 March 2020, we screened 2347 CR referrals, of which 908 were eligible and 382 were randomized (*Figure 1*). Despite reaching the revised recruitment target, the intervention and follow-up of the final 31 participants could not be completed due to the Covid-19 pandemic, leaving a sample of $n = 290$ at the 8 week primary outcome timepoint. The Covid-19 pandemic also prevented completion of 12 month follow-ups scheduled after 23 March 2020, leaving a sample of $n = 147$ at the 12 month timepoint. Of 382 participants at baseline, 187 (49%) were randomized to HIIT and 195 to (51%) MISS (*Figure 1*). Mean age was 59 years (SD, 9.6), and there were more male ($n = 356$, 93%) and White participants ($n = 333$, 87%) (*Table 1*). Participants in both arms were similar in terms

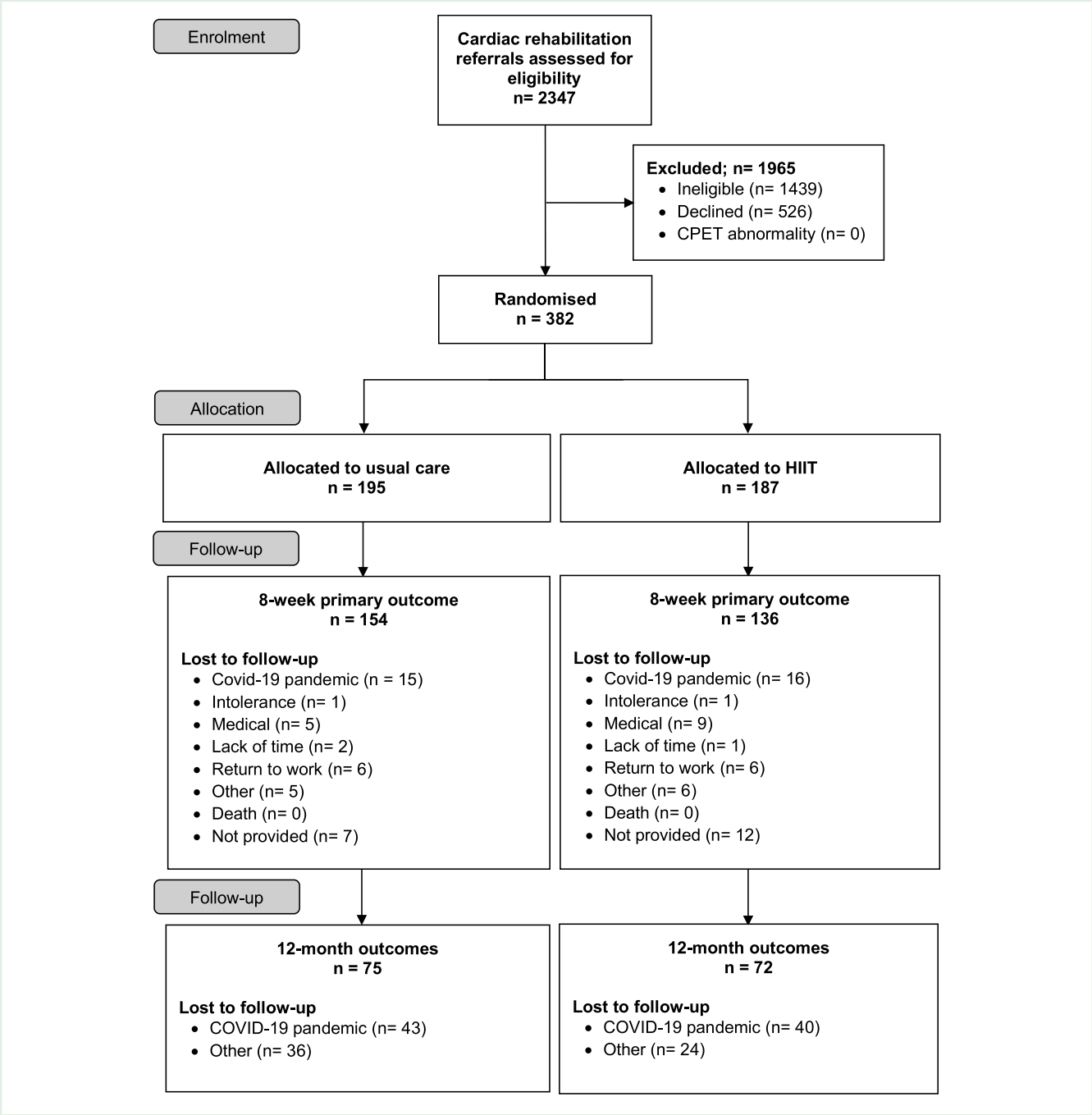

Figure 1 Study flowchart.

of baseline characteristics and treatment received. There were no major changes in medication during the intervention period.

Primary outcome: cardiorespiratory fitness

The primary outcome, $VO_{2\ peak}$, was similar at baseline in the HIIT and MISS arms (19.45 [SD, 5.40] $mL.kg^{-1}.min^{-1}$ vs. 19.63 [SD, 4.81]) (*Table 2*, *Figure 2A*). After the 8 week intervention, $VO_{2\ peak}$ improved more in the HIIT arm than in the MISS arm (mean change from baseline to 8 weeks of 2.37 vs. 1.32 $mL.kg^{-1}.min^{-1}$, *Table 3*). The difference of the mean change between the two arms was 1.06 $mL.kg^{-1}.min^{-1}$ (95% CI, 0.39–1.72; $P = 0.002$). The difference remained statistically significant after adjusting for age, sex, and study site (estimated difference, 1.04 $mL.kg^{-1}.min^{-1}$; 95% CI, 0.38–1.69; $P = 0.0021$). However, the difference was not statistically significant at 12 months post-baseline (estimated difference, 0.69 $mL.kg^{-1}.min^{-1}$; 95% CI, −0.43–1.82; $P = 0.23$). The treatment effect estimate obtained at the primary outcome timepoint using multiple imputation was consistent with other estimates (estimated difference, 1.05 $mL.kg^{-1}.min^{-1}$; 95% CI, 0.37–1.74; $P = 0.003$). Exploratory subgroup analyses indicated that HIIT improved $VO_{2\ peak}$ more than MISS at the 8 week timepoint for participants

Table 1 Demographics and baseline characteristics of study population. Values are numbers (percentages) unless stated otherwise

	MISS ($n = 195$)	HIIT ($n = 187$)	All ($n = 382$)
Demographics			
Age (yrs), mean (SD)	59.0 (9.9)	58.6 (9.2)	58.8 (9.6)
Sex:			
Male	180 (92.3)	176 (94.1)	356 (93.2)
Female	15 (7.7)	11 (5.9)	26 (6.8)
BMI (kg/m^2)	28.9 (4.1)	29.1 (4.5)	29.0 (4.3)
Ethnicity:			
White	170 (87.2)	166 (88.8)	336 (88.5)
Asian	20 (10.3)	17 (9.1)	37 (9.7)
Black	3 (1.5)	0 (0)	3 (0.8)
Other	2 (1.0)	4 (2.1)	6 (1.6)
Site:			
Coventry	118 (60.5)	115 (61.5)	233 (61.0)
Caerphilly	51 (26.2)	47 (25.1)	98 (25.7)
Hull	26 (13.3)	25 (13.4)	51 (13.4)
Diagnosis:			
STEMI	74 (37.9)	80 (42.8)	154 (40.3)
NSTEMI	72 (36.9)	66 (35.3)	138 (36.1)
Angina	46 (23.6)	36 (19.3)	82 (21.5)
Other	3 (1.5)	5 (2.7)	8 (2.0)
Time since event (days), median (IQR)	33 (20–45)	34 (20–50)	33 (20–52)
Treatment:			
Primary PCI	133 (68.2)	127 (67.9)	260 (68.1)
Elective PCI	25 (12.8)	25 (13.4)	50 (13.1)
CABG	29 (14.9)	23 (12.3)	52 (13.6)
Medical	8 (4.1)	10 (5.3)	18 (4.7)
Other	0 (0.0)	2 (1.1)	2 (1.0)
Medication:			
Beta-blocker	177 (90.1)	168 (89.8)	345 (90.3)
Anti-hypertensive	147 (75.4)	147 (78.6)	294 (77.0)
Anti-platelet	191 (98.0)	180 (96.3)	371 (97.1)
Statin	190 (97.4)	175 (93.6)	365 (95.6)
Anti-anginal	12 (6.2)	5 (2.5)	17 (4.5)
Diuretic	14 (7.2)	13 (7.0)	27 (7.1)
CVD risk factors:			
Hypertension	86 (44.1)	78 (41.7)	164 (42.9)
Family history	93 (47.7)	83 (44.4)	176 (46.1)
Dyslipidaemia	90 (46.2)	94 (50.3)	184 (48.2)
Mental health	37 (19.0)	27 (14.4)	64 (16.8)
Type II diabetes	30 (15.4)	21 (11.2)	51 (13.4)
Smoking:			
Never	73 (37.4)	82 (43.9)	155 (40.6)
Former	94 (48.2)	79 (42.3)	173 (45.3)
Current	28 (14.4)	23 (12.3)	51 (13.4)
Excess alcohol	24 (12.3)	19 (10.2)	43 (11.3)
Comorbidities:			
Musculoskeletal	73 (37.4)	74 (39.6)	147 (38.5)
Cerebrovascular	5 (2.6)	1 (0.5)	6 (1.6)
Peripheral vascular	2 (1.0)	1 (0.5)	3 (0.8)
Respiratory	19 (9.7)	20 (10.7)	39 (10.2)
Neurological	2 (1.0)	3 (1.6)	5 (1.3)
Cancer	14 (7.2)	10 (5.6)	24 (6.3)

Abbreviations: HIIT, high-intensity interval training; MISS, moderate-intensity steady-state training; SD, standard deviation; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; CVD, cardiovascular disease.

with ST elevation myocardial infarction (STEMI)/non-ST elevation myocardial infarction (NSTEMI) or CABG but not for elective PCI (see Supplementary material online, *Table S3*). Individual VO_{2peak} responses to HIIT and MISS are shown in *Figure 2C*. The SD_{IR} for both HIIT (2.60, 95% CI 1.90–3.15) and MISS (2.03, 95% CI 1.21–2.61) were above the MCID, with 55% of individual responses in the HIIT and 34% in the MISS groups exceeding the 75% probability threshold for a true positive response.

Secondary outcomes

$VO_{2\ AT}$ improved more at 8 weeks in HIIT compared with MISS (1.86 vs. 0.66 mL.kg^{-1}.min^{-1}; estimated difference, 1.20 mL.kg^{-1}.min^{-1}; 95% CI, 0.76–1.64; $P < 0.0001$), but this difference was not significant at 12 months (*Table 2*; *Figure 2B*). There was no difference between arms for the change in resting heart rate, blood pressure, or EQ-5D-5L from baseline to 8 week or 12 month follow-up (*Table 3*). Likewise, there was no difference between arms for left ventricular structure or function (see Supplementary material online, *Tables S4* and *S5*) or biochemical cardiovascular disease risk markers (*Table 3*) at 8 week follow-up. At 12 month follow-up, serum triglycerides reduced more in the HIIT arm compared with MISS (estimated adjusted difference, 0.21 mmol/L; 95% CI, 0.005–0.41; $P = 0.047$). However, values were within the normal clinical range at all measurement timepoints for both trial arms.

Adherence, tolerability, and fidelity

In total, 2288 sessions were completed in the HIIT arm and 2575 in the MISS arm. Of the 16 prescribed sessions, at least 13 (>80% of sessions) were completed by 75% of participants in the HIIT arm and 84% of participants in the MISS arm. In the per-protocol analysis (see Supplementary material online, *Table S1*), the proportion of 'non-completers'/'completers' (i.e. < or ≥13 (80%) sessions attended) by treatment arm was not statistically different; 15/155 MISS vs. 24/136 HIIT (chi-squared $P = 0.78$, results not shown). However, there was a statistically significant difference in $VO_{2\ peak}$ between HIIT and MISS at 8 week follow-up for those who completed at least 13 sessions.

The mean HR achieved for all participants over all monitored sessions (single sessions in weeks two, four, six, and eight) was 92.6 (SD, 11.6) $\%HR_{max}$ in the HIIT arm and 83.2 (SD, 10.3) $\%HR_{max}$ in the MISS arm ($P < 0.0001$). In the HIIT arm, 76% of HIIT sessions were completed above $85\%HR_{max}$. In contrast, in the MISS arm, only 45% of sessions were conducted within the prescribed range (60–80% HR_{max}) and 55% above (*Figure 3*). Mean peak RPE was 15.2 (SD, 2.0) in the HIIT arm and 12.7 (SD, 1.4) for the MISS arm ($P < 0.0001$) (*Figure 3*). Exercise training was performed at a mean of 96 (SD,

Table 2 Summary of cardiopulmonary, biochemical, and quality of life outcomes at baseline, 8 weeks, and 52 weeks by treatment arms. Values are means (standard deviations) unless stated otherwise

	MISS ($n = 195$)			HIIT ($n = 187$)		
	Baseline	8 weeks	52 weeks	Baseline	8 weeks	52 weeks
Primary outcome						
$VO_{2\ peak}$ ($mL.kg^{-1}.min^{-1}$)	19.63 (4.81)	20.84 (5.19)	21.54 (4.86)	19.45 (5.40)	21.85 (5.81)	21.75 (6.28)
Secondary outcomes						
Cardiopulmonary						
$VO_{2\ AT}$ ($mL.kg^{-1}.min^{-1}$)	12.07 (2.57)	12.73 (2.93)	12.87 (3.14)	11.91 (3.13)	13.77 (3.64)	13.15 (4.40)
HR_{rest} ($b.min^{-1}$)	62.26 (10.24)	60.83 (10.36)	60.83 (9.82)	62.81 (10.49)	60.52 (10.20)	60.83 (9.55)
SBP_{rest} (mmHg)	125.38 (17.63)	126.56 (17.15)	129.84 (18.43)	125.40 (15.28)	125.94 (14.42)	127.00 (17.92)
DBP_{rest} (mmHg)	80.80 (10.87)	81.03 (10.70)	81.83 (10.92)	81.24 (10.63)	79.99 (9.20)	81.30 (9.04)
Biochemistry						
Total CHOL (mmol/L)	3.44 (0.81)	3.51 (0.77)	3.67 (0.85)	3.52 (0.77)	3.58 (0.80)	3.60 (0.78)
LDL (mmol/L)	2.44 (0.80)	2.42 (0.72)	2.52 (0.86)	2.49 (0.72)	2.48 (0.78)	2.44 (0.79)
HDL (mmol/L)	0.99 (0.25)	1.09 (0.27)	1.15 (0.30)	1.04 (0.22)	1.10 (0.24)	1.16 (0.26)
Ratio (total CHOL : HDL)	3.63 (1.21)	3.36 (0.92)	3.40 (1.19)	3.49 (0.87)	3.38 (0.99)	3.24 (1.09)
Triglycerides (mmol/L)	1.66 (0.92)	1.51 (0.68)	1.69 (0.83)	1.62 (0.76)	1.55 (0.81)	1.45 (0.73)
hs-CRP (mg/L)	3.13 (4.43)	2.14 (4.97)	1.31 (1.60)	2.65 (5.40)	1.67 (3.35)	1.45 (3.43)
eGFR ($mL/min/1.73\ m^2$)	81.75 (17.30)	82.65 (16.67)	79.85 (14.49)	82.70 (16.9)	82.34 (17.08)	81.26 (20.17)
Quality of life						
EQ-5D-5L	0.84 (0.15)	0.90 (0.11)	0.89 (0.11)	0.83 (0.15)	0.90 (0.11)	0.90 (0.12)
EQ-5D-5L (VAS)	71.01 (19.71)	83.06 (11.67)	86.11 (9.92)	70.80 (17.75)	85.11 (10.55)	86.83 (10.30)

Abbreviations: HIIT, high-intensity interval training; MISS, moderate-intensity steady-state training; VO_2, oxygen uptake; AT, anaerobic threshold; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; VAS, visual analogue scale.

18.9) %PPO in the HIIT arm. Not all ergometers (rower, cross-trainer) provided workload in Watts. Therefore, we were not able to accurately quantify PPO in the MISS group.

Safety

Further to baseline CPET, no participants were excluded due to identification of exercise-induced ischaemia or haemodynamic compromise. There were five serious adverse events (three in the HIIT arm, one in the MISS arm, and one pre-randomization). One event that occurred during a HIIT session required hospitalization due to chest pain related to new-onset atrial fibrillation and was deemed to be *possibly related* to exercise. Of the other four serious adverse events, three (two in the HIIT arm, one in the MISS arm) occurred at participant's homes and were *not related* to the trial. All three required hospitalization: ischaemic stroke, chest pain due to pericarditis, and non-ischaemic cardiac arrest requiring pacemaker implantation. The final serious adverse event was identification of a left ventricular thrombus (pre-randomization), requiring outpatient cardiology review. Of the five participants experiencing serious adverse events, three were withdrawn from the trial. There were no unexpected adverse events in either trial arm.

Discussion

In adults with stable CAD attending CR in the UK, HIIT was superior to MISS exercise training for improving cardiorespiratory fitness, an important prognostic clinical outcome.[3,4] At the primary outcome time-point (8 weeks), the change in $VO_{2\ peak}$ from baseline was 1.04 $mL.kg^{-1}.min^{-1}$ greater in the HIIT arm than in the MISS arm. This value is clinically meaningful, reported to be equivalent to a reduction in premature mortality of approximately 15%.[5,29] Moreover, the percentage of participants showing a positive response was markedly higher in HIIT compared with MISS. In addition to demonstrating a clinical advantage over MISS, HIIT was safe and well tolerated. Only one serious adverse event (new-onset atrial fibrillation) was possibly related to exercise in the HIIT arm, and dropout due to intolerance was similar in both trial arms. At neither 8 weeks nor 12 months did we observe any clinically meaningful differences between HIIT and MISS for cardiovascular disease risk markers, left ventricular structure or function, or HRQoL.

As a direct representation of the ability to efficiently perform and sustain everyday activities, we objectively measured $VO_{2\ AT}$. The HIIT intervention improved this measure by 35% more than MISS at 8 week follow-up, representing a tangible functional gain. In combination with the lack of positive or negative difference between groups in left ventricular structure or function, these data confirm that the improvement in $VO_{2\ peak}$ was likely due to peripheral adaptation, rather than centrally mediated.

Systematic reviews and meta-analyses have reported greater improvements in cardiorespiratory fitness with various formats of HIIT (predominantly high volume) compared with MISS.[32–35] However, these include mostly small laboratory-controlled studies. As such, the magnitude of superiority of HIIT in our trial was smaller than previously reported (~1.7 $mL.kg^{-1}.min^{-1}$). This reflects the pragmatic nature of our trial, with interventions delivered in NHS CR services by clinical practitioners, not research staff. Nevertheless, whilst our trial was powered to observe a between groups difference of 1.5 $mL.kg^{-1}.min^{-1}$ in favour of HIIT, the observed difference of 1.04 $mL.kg^{-1}.min^{-1}$ is still

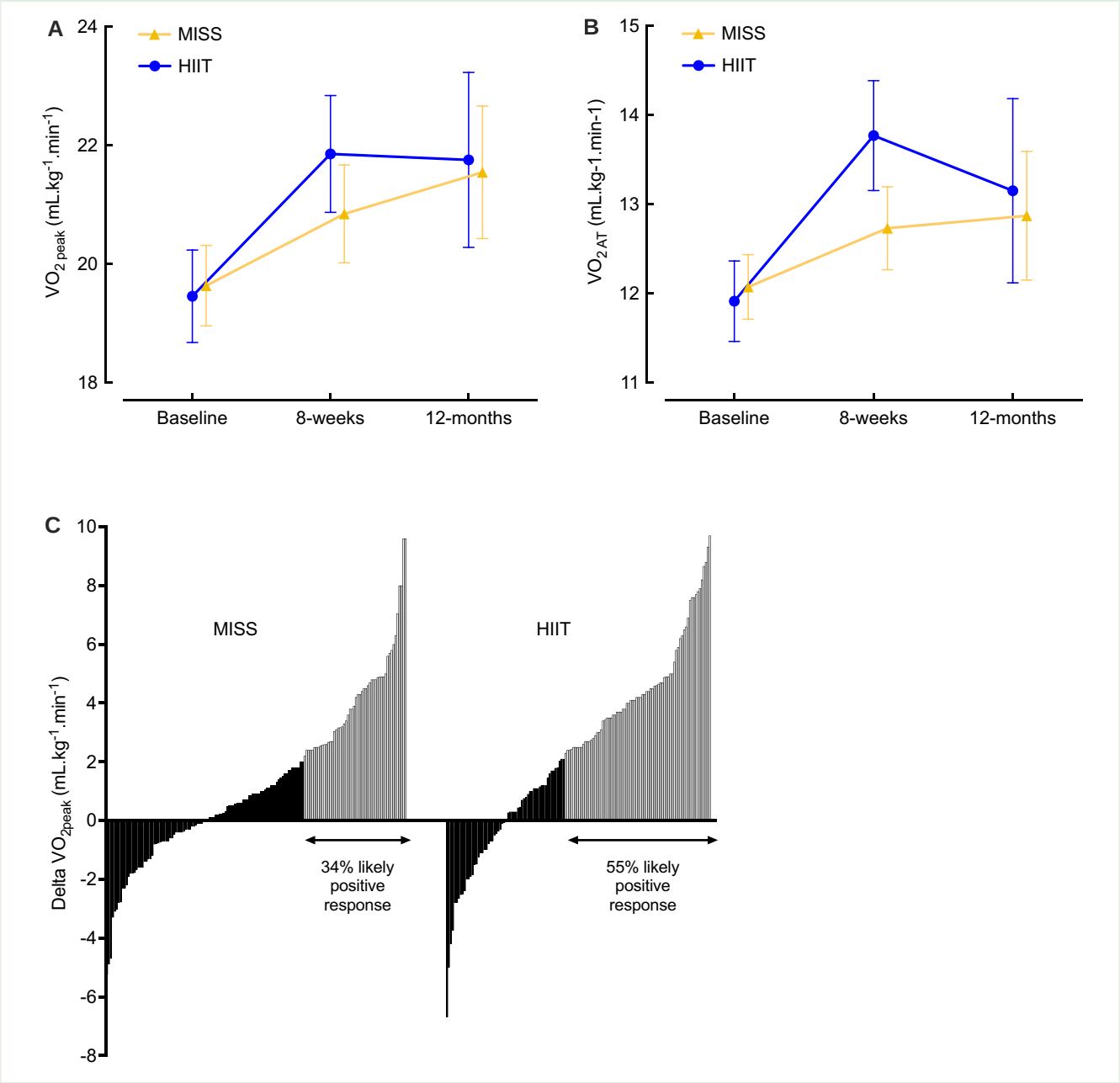

Figure 2 (*A*) $VO_{2\ peak}$ at baseline, 8 weeks, and 12 months. (*B*) $VO_{2\ AT}$ at baseline, 8 weeks, and 12 months. Values are mean (SD). (*C*) Individual $VO_{2\ peak}$ change scores with HIIT and MISS. Data represent those individuals who, after accounting for the interindividual variance in response, and the technical error of measurement, may be considered a positive responder beyond the minimal clinical important difference to the intervention (i.e. above the 75% likelihood threshold calculated using (Hopkins W. Precision of the estimate of a subject's true value (Excel spreadsheet). Available at: https://www.sportsci.org/resource/stats/xprecisionsubject.xls)).

clinically meaningful,[29] and this is the only pragmatic trial to demonstrate this. Estimates from the per-protocol analyses were consistent with these findings.

An important observation from our trial is the difference in exercise intensity recorded between the two trial arms. We rigorously assessed fidelity which indicated that exercise was consistently performed at a higher intensity in the HIIT arm compared with MISS, even despite the MISS arm exceeding the recommended UK guidelines. This confirms the tolerability and acceptability of the low-volume 1 min interval HIIT model in this population as reported in smaller studies and meta-analyses.[36] In contrast, notable previous studies using a 4 min interval HIIT model reported little difference in exercise intensity between HIIT and MISS, due primarily to the inability of participants to achieve the prescribed exercise intensity for the duration of the longer HIIT intervals.[12,13] The clinical effectiveness, tolerability, and safety of the 1 min interval protocol suggest that this model is suitable for CR programmes.

Similar to the majority of exercise trials, we focused on the overall treatment effect for the entire study population. However, a

Table 3 Unadjusted and adjusted difference of mean change from baseline to follow-up timepoints between treatment arms for cardiopulmonary, biochemical, and quality of life outcomes

	Baseline to 8 weeks				Baseline to 52 weeks			
	Unadjusted difference (95% CI)	P	Adjusted difference (95% CI)	P	Unadjusted difference (95% CI)	P	Adjusted difference (95% CI)	P
Primary outcome								
$VO_{2\ peak}$ ($mL.kg^{-1}.min^{-1}$)	1.06 (0.39–1.72)	0.002	1.04 (0.38–1.69)	0.002	0.76 (−0.40–1.92)	0.20	0.69 (−0.43, 1.82)	0.23
Secondary outcomes								
Cardiopulmonary								
$VO_{2\ AT}$ ($mL.kg^{-1}.min^{-1}$)	1.21 (0.76–1.65)	<0.0001	1.20 (0.76–1.64)	<0.0001	0.27 (−0.57–1.10)	0.53	0.30 (−0.55, 1.16)	0.49
HR_{rest} ($b.min^{-1}$)	0.21 (−1.55–1.96)	0.82	0.31 (−1.44–2.06)	0.73	−0.33 (−0.882–5.17)	0.17	−0.24 (−2.83, 3.31)	0.88
SBP_{rest} (mmHg)	1.97 (−2.10–6.04)	0.34	1.99 (−2.11–6.09)	0.34	−3.08 (−3.44–9.61)	0.36	−2.97 (−3.68, 9.62)	0.38
DBP_{rest} (mmHg)	1.13 (−1.44–3.70)	0.39	1.13 (−1.47–3.73)	0.40	−1.24 (−2.85–5.33)	0.55	−1.18 (−2.94, 5.30)	0.58
Biochemistry								
Total CHOL (mmol/L)	0.04 (−0.10–0.17)	0.60	0.02 (−0.11–0.15)	0.79	0.23 (−0.01–0.47)	0.06	0.22 (−0.02–0.46)	0.08
LDL (mmol/L)	0.05 (−0.08–0.17)	0.46	0.03 (−0.09–0.16)	0.62	0.23 (−0.002–0.46)	0.05	0.22 (−0.01–0.46)	0.06
HDL (mmol/L)	0.01 (−0.02–0.04)	0.50	0.01 (−0.02–0.05)	0.39	0.001 (−0.06–0.06)	0.99	0.005 (−0.06–0.07)	0.86
Ratio (total CHOL : HDL)	−0.001 (−0.16–0.16)	0.99	−0.02 (−0.17–0.14)	0.85	0.13 (−0.19–0.45)	0.42	0.12 (−0.20–0.44)	0.45
Triglycerides (mmol/L)	−0.03 (−0.17–0.12)	0.71	−0.03 (−0.18–0.11)	0.67	0.21 (0.01– 0.42)	0.04	0.21 (0.005–0.41)	0.047
hs-CRP (mg/L)	0.03 (−1.32–1.38)	0.97	−0.05 (−1.42–1.31)	0.94	−1.10 (−2.53–0.34)	0.14	−1.12 (−2.56–0.32)	0.13
eGFR (mL/min/1.73 m^2)	−11.60 (−33.8–10.6)	0.31	−12.35 (−34.8–10.1)	0.28	0.55 (−4.19–5.29)	0.82	0.37 (−4.28–5.01)	0.88
Quality of life								
EQ-5D-5L	0.01 (−0.02–0.04)	0.62	0.01 (−0.027–0.04)	0.71	0.029 (−0.01–0.07)	0.20	0.02 (−0.02–0.07)	0.27
EQ-5D-5L (VAS)	1.92 (−2.04–5.88)	0.34	1.65 (−2.21–5.50)	0.40	1.27 (−4.15–6.70)	0.65	1.34 (−3.96–6.63)	0.62

Adjusted difference and corresponding 95% confidence interval (CI) and *P*-value analyses were performed with the generalized linear model (GLM) with usual care as reference factor and covariates in the adjusted model; age (continuous), sex (categorical), and study site (categorical). Positive values indicate the superiority of high-intensity interval training (HIIT); negative values indicate the superiority of usual care. Abbreviations: HIIT, high-intensity interval training; MISS, moderate-intensity steady-state training; VO_2, oxygen uptake; AT, anaerobic threshold; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHOL, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; VAS, visual analogue scale.

noteworthy finding from our study is the significant heterogeneity in the $VO_{2\ peak}$ response to both HIIT and MISS. The range in response from −6.7 to +9.7 $mL.kg.min^{-1}$ across both arms suggests that the impact of exercise training is not uniform across individuals. Although prescribing HIIT, as opposed to MISS, reduced the number of low or negative responders, whether this difference relates to the greater physiological stimulus associated with HIIT or is driven by other mechanisms is not clear from our study. Irrespective, these data suggest that programmes adopting HIIT will likely be more successful in improving VO_{2peak} on a per-patient basis than those using moderate-intensity prescriptions. Importantly, these data also highlight the need to explore a more personalized approach to exercise prescription in future studies in order to examine whether it is possible to further optimize patient outcomes.

In the absence of definitive evidence, the adoption of HIIT in CR has remained contentious in some countries. Concerns regarding acceptability, tolerability, and safety have prevented widespread implementation. Providing that all usual screening and assessment procedures are undertaken, findings from our trial should reassure CR practitioners and patients that this modality of exercise is both effective and safe for adults with stable CAD attending supervised CR. Whilst we undertook maximal exercise testing with all 382 participants at baseline, no participants were deemed ineligible for HIIT further to ECG, blood pressure, and respiratory gas analyses. This suggests that by applying standard screening criteria[18] and HIIT-specific objective and subjective prescription and monitoring recommendations as detailed by Taylor *et al.*,[37] HIIT may be prescribed without obligatory maximal exercise testing, something that is favourable given that CPET is not available in many rehabilitation settings around the world. High-intensity interval training is simple to implement, and the effectiveness of the intervention confirms its value as an additional tool in CR programmes. This is particularly pertinent in light of the apparent diminishing mortality benefits of CR exercise training in the context of contemporary medical and pharmacological CAD management.[1,38] With an evident decline in $VO_{2\ peak}$ between 8 weeks and 12 months in both trial arms, it is clear that additional behavioural strategies and structured physical activity provision are required to sustain the benefits achieved with HIIT in CR. Furthermore, given the lack of difference between HIIT

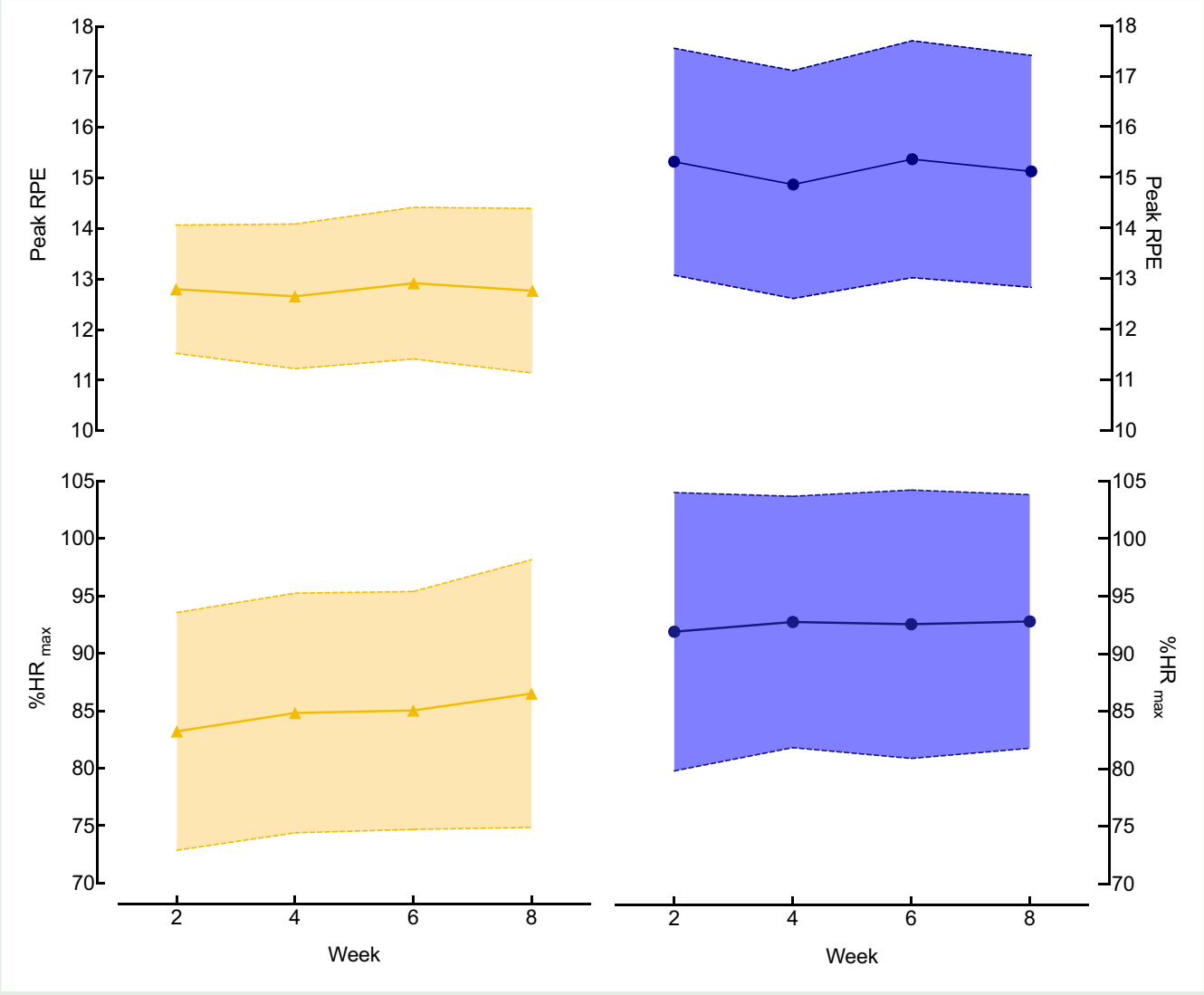

Figure 3 Mean $\%HR_{max}$ (bottom) and RPE (top) achieved during single MISS (left) and HIIT (right) sessions at weeks two, four, six, and eight of the exercise training programme. At all timepoints, mean $\%HR_{max}$, and RPE were statistically greater in HIIT vs. MISS. Values are mean (SD).

and MISS in cardiovascular disease risk markers, left ventricular structure or function, or HRQoL, it is apparent that HIIT does not meaningfully impact positively or negatively on these outcomes when compared with MISS. Future work should consider longer and/or higher-volume exercise programmes, or alternative intervention strategies, to examine how these outcomes may be moderated. The relatively low exercise volume in our trial, whilst effective at improving $VO_{2\ peak}$, may have been insufficient to impact these outcomes.

Strengths and limitations

We conducted the largest pragmatic multi-centre RCT of HIIT vs. MISS to date. Interventions were delivered by CR, not research staff, and outcome assessors were blinded to group allocation. This is the first trial to adopt this approach and to report a clinically meaningful benefit of HIIT over MISS using a gold-standard, objective measure of cardiorespiratory fitness. Data from our trial are relevant to CR programmes around the world.

Limitations relate predominantly to the impact of the Covid-19 pandemic. We were unable to follow up 31 participants at the 8 week primary outcome timepoint, and data were missing from 83 participants at 12 months. The amount of missing data increased uncertainty regarding 12 month results. Finally, our trial population was predominantly White male, reducing the confidence with which we can generalize these data to different demographics. However, these data are not too dissimilar to the general CR population in the UK (e.g. 79% White British and 71% male),[39] and our cohort represented those primarily from lower socioeconomic groups.

Conclusion

We report convincing evidence of the clinical superiority of HIIT compared with MISS CR exercise training for improving objectively measured cardiorespiratory fitness, an important prognostic clinical endpoint in adults with CAD. Further, we confirmed that HIIT is well tolerated, and safe, and can be implemented and delivered within standard CR services. Low-volume HIIT should be routinely considered as an adjunct or alternative to MISS, and future guidelines should incorporate these recommendations.

Author contribution

G.M. and R.S. were responsible for the conception of the study. G.M., R.S., S.N., L.I., P.B., R.T.E., M.H., and J.M.C. designed the trial. G.M., R.S., S.N., L.I., P.B., R.P., B.B., and T.H. were responsible for trial oversight. R.P., B.B., S.B., S.E., H.H., T.L., F.O., J.M.C., R.T.E., A.D., and S.M. collected data. S.W.H., T.H., O.F., N.H., and R.T.E. conducted the analysis. G.M. drafted the manuscript. All authors interpreted the data, critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* Online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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