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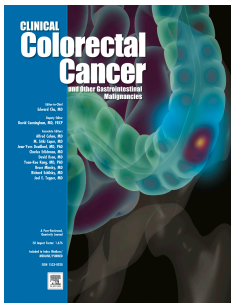


Cardiorespiratory fitness and body composition responses to different intensities and frequencies of exercise training in colorectal cancer survivors

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**Title:**

Cardiorespiratory fitness and body composition responses to different intensities and frequencies of exercise training in colorectal cancer survivors

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Exercise for colorectal cancer survivors

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**Keywords:**

Exercise oncology; high-intensity exercise; physical activity; fat mass; lean mass

**Abbreviations:**

DXA: dual energy x-ray absorptiometry

HIIE: high-intensity interval exercise

HIIE-T: high-intensity interval exercise-tapered

$HR_{peak}$: peak heart rate

MICE: moderate-intensity continuous exercise

$\dot{V}O_2peak$: cardiorespiratory fitness

**Micro-abstract:**

The optimal exercise intensity and frequency to promote clinically significant improvements in cardiorespiratory fitness and body composition for colorectal cancer survivors is unknown. In a group of colorectal cancer survivors (n=57), high intensity interval exercise promoted superior benefits to the current moderate intensity exercise guidelines, even with a substantially reduced training frequency and following short-term training withdrawal.

**Abstract:**

Introduction: Deteriorations in cardiorespiratory fitness ($\dot{V}O_2$peak) and body composition are associated with poor prognosis following colorectal cancer treatment. However, the optimal intensity and frequency of aerobic exercise training to improve these outcomes in colorectal cancer survivors is unknown. Methods: This trial compared eight weeks of moderate intensity continuous exercise [MICE; 50min; 70% peak heart rate ($HR_{peak}$); 24 sessions], with high intensity interval exercise (HIIE; 4x4min; 85-95% $HR_{peak}$) at an equivalent (HIIE; 24 sessions) and tapered frequency (HIIE-T; 16 sessions) on $\dot{V}O_2$peak, lean and fat mass, measured at baseline, four, eight and twelve weeks. Results: Increases in $\dot{V}O_2$peak were significantly greater following both four ($+3.0 ml \cdot kg^{-1} \cdot min^{-1}$, p=0.008) and eight ($+2.3 ml \cdot kg^{-1} \cdot min^{-1}$, p=0.049) weeks of HIIE compared with MICE. After eight weeks, there was a significantly greater reduction in fat mass after HIIE compared to MICE (-0.7kg, p=0.038). Four weeks following training, the HIIE group maintained elevated $\dot{V}O_2$peak ($+3.3 ml \cdot kg^{-1} \cdot min^{-1}$, p=0.006) and reduced fat mass (-0.7kg, p=0.045) compared to the MICE group, with $\dot{V}O_2$peak in the HIIE-T also being superior to the MICE group ($+2.8 ml \cdot kg^{-1} \cdot min^{-1}$, p=0.013). Conclusions: Compared to MICE, HIIE promotes superior improvements and short-term maintenance of $\dot{V}O_2$peak and fat mass improvements. HIIE training at a reduced frequency also promotes maintainable cardiorespiratory fitness improvements. In addition to promoting accelerated and superior benefits to the current aerobic exercise guidelines, HIIE promotes clinically relevant improvements even with a substantial reduction in exercise training and for a period following withdrawal.

**Clinical Practice Points**

*What is already known about this topic?*

There is a strong relationship between cardiorespiratory fitness, body composition and clinical prognosis following colorectal cancer. Whilst exercise has been shown to improve these outcomes, the optimal intensity

and frequency of exercise to maximise clinically relevant improvements for colorectal survivors remains to be determined.

*What are the new findings?*

When compared to the current aerobic guidelines (moderate intensity continuous exercise), eight weeks of high intensity interval exercise (HIIE) promoted accelerated and superior improvements in cardiorespiratory fitness and reductions in fat mass. Importantly following complete withdrawal of the training intervention for four weeks, participants who completed HIIE maintained these improvements without an additional training stimulus. Furthermore, a tapered HIIE training program (training frequency reduced by two-thirds for the latter half of the intervention) was sufficient to maintain superior increases in cardiorespiratory fitness following training cessation relative to the group prescribed the current guidelines.

*How might it impact clinical practice in the future?*

Collectively the results of this investigation suggest that in addition to promoting accelerated and superior benefits to the current moderate intensity exercise guidelines in colorectal cancer survivors, HIIE can also promote clinically relevant improvements even with a substantial reduction in exercise training and for a period following complete training withdrawal. This finding is particularly important given the difficulties promoting long-term adherence to exercise programs in cancer survivors; these results suggest that HIIE may be a novel approach to promote health-related improvements with a substantially reduced time commitment in colorectal cancer survivors.

***Introduction***

Deteriorations in cardiorespiratory fitness [1-3] and body composition (decreases in lean mass [4] and increases in fat mass [5, 6]) are independently associated with poor prognosis following colorectal cancer diagnosis and treatment. Substantial reductions in $\dot{V}O_2$peak have been shown to predict both morbidity [1] and cancer-specific mortality [2, 3]. Specific to the musculoskeletal system, decreased lean muscle mass is a prevalent comorbidity following colorectal cancer diagnosis that can predict rates of disease-free and overall survival [4]. Decreases in muscle mass are often masked by increases in fat mass [7], which is independently associated with a range of adverse clinical outcomes, including lower overall survival in colorectal cancer patients [5, 6]. Cardiorespiratory fitness and body composition are thus clinically important prognostic measures that significantly predict long-term outcomes for survivors.

Given the substantial impairments in cardiorespiratory fitness and body composition following treatment for colorectal cancer, there is a clear need for effective interventions to ameliorate these deteriorations. Though aerobic exercise training improves $\dot{V}O_2$peak, which can subsequently improve prognosis [8], meta-analyses show that longer-term (>8 weeks) interventions of moderate-to-vigorous intensity exercise training promote only modest (+2.9ml$\cdot$kg$^{-1}\cdot$min$^{-1}$) $\dot{V}O_2$peak improvements in cancer survivors [9]. In comparison to moderate intensity continuous exercise (MICE), high intensity interval exercise (HIIE) has been shown to offer superior cardiorespiratory fitness improvements in healthy adults [10] and patients with lifestyle-induced cardiometabolic disease [11]. Potential similar relationships between exercise intensity and changes in cardiorespiratory fitness and body composition in cancer survivors have revealed no clear consensus regarding the superiority of any specific exercise intensity [12-16]. As with any novel therapeutic prescription, defining the optimal exercise intensity to promote clinically relevant improvements in cardiorespiratory fitness and body composition should encompass factors beyond the magnitude of change, to include the time-course and reversibility of changes in response to the prescription, with the latter factors yet to be fully investigated in cancer survivors. To date, studies examining the influence of exercise intensity on variables in cancer survivors have only compared pre- and post-training measures; the time-course of these changes have not been evaluated. Equivalent long term changes between HIIE and MICE [13-15] does not preclude differences existing between the rates of physiological adaptation, as we have previously shown that HIIE promotes improvements in $\dot{V}O_2$peak and reductions in fat mass in response to short term training (four weeks) in colorectal cancer survivors [12]. Elucidation of potential differences in the velocity of adaptations provides important information regarding the duration of prescription required for improvements in response to exercise at different intensities.

In addition to the effectiveness in reversing the adverse changes following colorectal cancer, interventions also need to promote engagement by considering common barriers to participation in exercise programs. A 'lack of time' for exercising, when coupled with cancer-specific factors such as fatigue [17], emphasises the need to identify exercise interventions that can maximise the clinical benefits of exercise for colorectal cancer survivors whilst minimising barriers to participation due to social or disease-specific factors. The concept of tapering or reducing training volume (via reduction in exercise frequency, intensity or duration) is widely used to optimise athletic performance [18] and to maintain improvements in $\dot{V}O_2$peak [19]. Tapering may also be time-effective in the oncology setting, where improvements following an initial high-frequency loading period can be effectively maintained with a reduced training frequency. This may promote increased adherence to longer-term exercise programs due to the reduced training load and time commitment.

In addition to the within-intervention time course of changes, recent data suggest that supervised higher intensity exercise leads to more maintainable improvements in $\dot{V}O_2$peak when continued with a home-based prescription compared to MICE [15]. However whether adaptations are maintained at all following complete withdrawal of the training stimulus in response to differential exercise intensities is yet to be assessed. Establishing the magnitude and rate at which adaptations are lost will provide insight into whether exercise-induced improvements can be at all maintained when interruptions to longer term exercise programs occur, such as through non-adherence, clinical complications or social interruptions (e.g. travel).

The purpose of this study was to describe the time course of changes in cardiorespiratory fitness and body composition in responses to an eight-week (1) MICE intervention, (2) HIIE intervention of equivalent frequency, and (3) a HIIE intervention utilising a tapered frequency prescription in a cohort of colorectal cancer survivors. Short-term maintenance of these changes over four weeks was then assessed following withdrawal of the training interventions. It was hypothesised that when compared with MICE, both HIIE prescriptions would elicit greater improvements in $\dot{V}O_2$peak and body composition, and that these changes would be less reversible in the short-term following training completion.

***Methods***

This study was granted ethical approval by the Human Ethics Committee of The University of Queensland and is registered under the Australian and New Zealand Clinical Trials Registry (ACTRN12615000908538; www.anzctr.org.au). This study presents the entire approved trial and adds to data previously reported elsewhere [12], which was subsequently expanded since the time of publication.

Participants

Men and women previously diagnosed with colorectal cancer were recruited from Brisbane (Queensland, Australia) for this randomised controlled trial. Inclusion criteria were as follows: (i) aged ≥18 years old; (ii) ≥ one-month post-treatment for colorectal cancer and not anticipating undergoing treatment during the study period; and (iii) free of any musculoskeletal, neurological, respiratory, metabolic or cardiovascular conditions that may have prevented safe completion of the exercise demands of the study. Details of the recruitment processes have been reported elsewhere [12].

Study Protocol

Participants were required to obtain physician consent for participation in the program, and were individually screened via a medical history form and interview with the investigators to determine eligibility. At the first session, participants were provided with further details of the research program and afforded the opportunity to seek clarification relating to any aspects of the study, after which informed consent was obtained from all individual participants included in the study. Following this, participants completed a familiarisation session consisting of a test of peak oxygen consumption ($\dot{V}O_2$peak) to assess cardiorespiratory fitness. Seven days later, each participant completed a baseline testing session consisting of an assessment of body composition and a $\dot{V}O_2$peak test. Prior to each testing session, participants were asked to: (i) consume plenty of water; (ii) abstain from caffeine and alcohol intake for 12 hours; and (iii) avoid any high, vigorous, or unaccustomed moderate intensity physical activity for 48 hours. External weekly physical activity behaviours of participants were measured at baseline using the Godin leisure-time exercise questionnaire [20]. Following baseline testing, a researcher independent to the study stratified the participants according to age (<55 or ≥55 years) and sex, and randomised participants via a computer generated random number assignment process to one of three groups: (1) MICE, (2) HIIE or (3) HIIE-tapered (HIIE-T). All groups trained three times per week for the initial four weeks. For the subsequent four-week period, the HIIE and MICE groups continued to train three times per week, whereas the HIIE-T group trained once a week. Mid- and endpoint testing, involving identical procedures to those used at baseline testing, was completed between three and seven days after four and eight weeks of training, respectively. All participants were instructed to maintain their normal diet and physical activity behaviours throughout the eight-week intervention, as well as for the four weeks immediately following the intervention when the specific training sessions prescribed were ceased. Participants were then re-tested four weeks following cessation of the eight-week interventions.

Outcome measures

$\dot{V}O_2$peak testing was completed using a cycle ergometer (Lode Excalibur Sport, Lode B.V., Groningen, Netherlands) and a portable metabolic cart system (ParvoMedics TrueOne 2400, Sandy, USA). Following a four-minute warm up at 50W, participants cycled at 60-70 revolutions.min$^{-1}$ with incremental 20-30W.min$^{-1}$ increases in resistance until volitional fatigue. $\dot{V}O_2$peak was recorded as the mean of the two highest 15-second $\dot{V}O_2$ epochs. Full details of this test have been reported elsewhere [12].

Subtotal (whole body minus the head) fat and lean masses were measured by dual energy x-ray absorptiometry (DXA; Hologic Discovery A, Waltham, MA). The coefficients of variation values in our laboratory for whole body fat and lean mass are <1.1%. Scans were conducted and analysed by two accredited DXA technicians; inter-tester analysis CV: subtotal fat mass=0.4%; subtotal lean mass=0.3%; subtotal body fat percentage=0.4%). Due to equipment malfunction a subset of baseline DXA scans were unavailable for 10 participants who were subsequently excluded from body composition analysis. Height and body mass were measured using a stadiometer (Seca, Birmingham, United Kingdom) and electronic scales (A & D Mercury, Pty Ltd, Thebarton, Australia), respectively.

Exercise Interventions

The MICE training protocol consisted of 50 minutes of cycling at 50-70% peak heart rate ($HR_{peak}$). The frequency and volume of MICE was consistent with the current aerobic physical activity guidelines for cancer survivors [21, 22]. HIIE training sessions involved a 10 minute warm up at 50-70% $HR_{peak}$ before the commencement of a four minute interval, cycling at 85-95% $HR_{peak.}$ Each interval was interspersed with a three minute period of active recovery, repeated four times for a total of 38 minutes for the session. Intervention feasibility (completion rates), safety (adverse events) and adherence were calculated as previously described [12].

Statistical Analysis

As the aim of this trial was to investigate efficacy outcomes, a per protocol approach was utilised rather than intention to treat. All data were analysed using SPSS (version 23.0; Chicago, IL). Linear mixed (fixed and random) modelling was used to assess changes over time and differences among intervention groups. Group, time, and group by time interaction were treated as fixed factors; participants were treated as a random factor with individual intercepts. Each model included sex as a covariate and was adjusted using the baseline value as a fixed continuous covariate as previously described [23, 24]. Model residuals were formally assessed for normality

by use of the Shapiro-Wilk test and visual inspection of histogram plots. Bonferroni pairwise adjustments were made for all subsequent comparisons. Statistical significance was set at an alpha of $p<0.05$.

***Results***

Participant flow through the intervention and characteristics for the 57 participants are reported in Figure 1 and Table 1, respectively. Details of the most commonly cited reasons for non-participation reported by eligible participants are also presented in Figure 1. Fewer women were randomised to the HIIE group (27.8%) compared to the HIIE-T (50.0%) and MICE (52.6%) groups. To account for any potential influence of this imbalance, all analyses included sex as a covariate, however it was not a significant ($p\geq0.05$) factor in any of the analyses. Intervention completion rates for participants within the HIIE, HIIE-T and MICE groups were 94.7%, 95.0% and 89.5%, respectively. A total of four participants withdrew prior to the completion of the intervention period (8 week time point) due to personal reasons (n=1), family commitments (n=2) or due to ongoing interruptions resulting from additional medical diagnostic testing for an unrelated condition (n=1). Seven participants were unable to be assessed at the follow up time point (within the stipulated 4±1 week timeframe) following completion of the intervention and therefore these data were absent at the 12-week time point. As assessed by the Godin questionnaire, there were no significant effects of group allocation ($p=0.203$), time point ($p=0.736$) or an interaction between these factors ($p=0.898$) on the exercise frequency index, weighted for the perceived intensity of the session. There were no severe adverse events as a result of exercise testing or training, and no additional adverse events to those previously detailed [12].

Cardiorespiratory fitness

Changes in $\dot{V}O_2$peak are displayed in Table 2. Both HIIE and HIIE-T showed superior increases in $\dot{V}O_2$peak after just 4 weeks of training compared to the MICE group at this time point (HIIE vs. MICE: $+3.0 ml \cdot kg^{-1} \cdot min^{-1}$, $p=0.008$; HIIE-T vs. MICE: $+2.3 ml \cdot kg^{-1} \cdot min^{-1}$, $p=0.030$). Improvements in $\dot{V}O_2$peak after eight weeks of HIIE were significantly greater than the improvements following MICE ($+2.3\ ml \cdot kg^{-1} \cdot min^{-1}$, $p=0.049$). Following the four-week withdrawal of the training stimulus, $\dot{V}O_2$peak in the HIIE and HIIE-T groups remained significantly higher than the MICE group (HIIE: $+3.3 ml \cdot kg^{-1} \cdot min^{-1}$, $p=0.006$; HIIE-T: $+2.8 ml \cdot kg^{-1} \cdot min^{-1}$, $p=0.013$). There were no significant ($p\geq0.05$) differences between the HIIE and HIIE-T groups at any time point.

Body composition

Lean mass and fat mass changes in response to each intervention are shown in Table 3. There were no significant ($p \geq 0.05$) between or within-group changes in lean mass for any group across the eight weeks of training. Following removal of the training stimulus, there was a significant increase in lean mass in the MICE group (+0.2kg, p=0.027), however this was not significantly different from either of the HIIE groups. The HIIE group demonstrated a significantly superior decrease in fat mass compared to the MICE group after eight weeks of training (-0.7kg, p=0.038) and this was maintained following four weeks without training (-0.7kg, p=0.045).

***Discussion***

This study compared the time course of changes in cardiorespiratory fitness ($\dot{V}O_2$peak) and body composition between HIIE and MICE, and the maintenance of these adaptations following a tapered training frequency as well as training cessation in colorectal cancer survivors. Compared to MICE (which aligns with current aerobic exercise-oncology guidelines), HIIE promoted superior improvements in $\dot{V}O_2$peak and reductions in fat mass following eight weeks of training. Relative to the MICE intervention, which had regressed to baseline following four weeks without training, superior $\dot{V}O_2$peak and fat mass changes were maintained in the HIIE group. Additionally, following withdrawal of the training intervention, $\dot{V}O_2$peak in the HIIE-T group also remained significantly elevated above the MICE group indicating improvements accrued following an initial high load HIIE prescription were maintained with a substantially reduced training requirement. In addition to the superior $\dot{V}O_2$peak and fat mass changes, these preliminary results indicate that prescription of HIIE for colorectal cancer survivors may also prevent regression of these adaptations during interruptions to longer term exercise-medicine programs and improve adherence due to the propensity for improvements in $\dot{V}O_2$peak with reduced training frequency.

The magnitude of $\dot{V}O_2$peak improvement ($+2.7 ml \cdot kg^{-1} \cdot min^{-1}$) following MICE, which equated to the aerobic component of the current physical activity guidelines for cancer survivors, was consistent with the improvements reported from a meta-analysis of predominantly moderate-to-vigorous intensity trials in cancer patients and survivors [9]. In comparison, the improvements from baseline following eight weeks of equivalent frequency HIIE training ($+5.2 ml \cdot kg^{-1} \cdot min^{-1}$) were significantly greater (p=0.049), with the velocity of adaptation also being superior in the HIIE group. No changes in $\dot{V}O_2$peak were observed after four weeks of MICE, whereas significant increases ($+4.2 ml \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$) constituting 81% of the total improvement in $\dot{V}O_2$peak occurred with HIIE during the initial four weeks, indicating accelerated $\dot{V}O_2$peak improvements in

response to short term HIIE. This finding confirms the efficacy of HIIE in producing rapid and significant improvements in cardiorespiratory fitness.

Lower levels of $\dot{V}O_2$peak are associated with elevated rates of cancer-specific mortality [2, 3]. Increasing cardiorespiratory fitness has been associated with significant reductions in cancer-specific mortality, which underscores the importance of the present findings [8]. Given the breadth of physiological impairments (cardiac output, endothelial and skeletal muscle function) following colorectal cancer diagnosis and treatment, it is not surprising that such a strong relationship with mortality exists given that $\dot{V}O_2$peak measures the integrated maximal function of these systems in response to exercise [25]. To contextualise the magnitude of the present $\dot{V}O_2$peak changes and their potential clinical relevance, data from the Cooper Center Longitudinal Study (n = 13,949) estimated that each 1-metabolic equivalent (MET; equivalent to 3.5 $ml.kg^{-1}.min^{-1}$) increase in cardiorespiratory fitness in a population of cancer patients was associated with a 10% [Hazard ratio=0.90 (0.84–0.97)] reduction in cancer-specific mortality and a 25% [Hazard ratio=0.75 (0.66–0.87)] reduction in the risk of cardiovascular disease mortality [3]. Additional data from the Aerobics Center Longitudinal Study (n = 13,930) reported similar relationships (albeit non-significant) between changes in cardiorespiratory fitness following diagnosis (rather than baseline values) [8]. A linear relationship was found between improvements in maximal METs and reduction in cancer specific mortality (p = 0.05), with each 1-MET increase being marginally associated with a 5% reduction in mortality (p = 0.10) [8]. Whilst it is not possible to directly estimate the potential magnitude of mortality risk reduction, the degree of $\dot{V}O_2$peak improvement after HIIE completed three times per week (HIIE = +5.2 $ml.kg^{-1}.min^{-1}$) or even at a tapered frequency (once per week; HIIE-T = +4.1 $ml.kg^{-1}.min^{-1}$) is likely to be clinically meaningful. Additionally, even following a 4-week withdrawal of the prescribed exercise, participants in both HIIE groups maintained their previous increases in $\dot{V}O_2$peak (HIIE=+4.2$ml\cdot kg^{-1}\cdot min^{-1}$; HIIE-T=+3.4$ml\cdot kg^{-1}\cdot min^{-1}$). Therefore including HIIE as part of exercise-medicine programs may provide substantial flexibility in programming frequency when promoting long-term maintenance of improvements in $\dot{V}O_2$peak. This includes the capacity to account for interruptions to exercise programs (e.g. clinical complications or travel) that may prevent either total or high frequency exercise participation without a complete regression of $\dot{V}O_2$peak improvements. In contrast, the present data indicate that whilst eight weeks of MICE significantly improves $\dot{V}O_2$peak (2.7$ml\cdot kg^{-1}\cdot min^{-1}$), longer duration MICE programs may be necessary to achieve improvements associated with clinically relevant reductions in mortality. This necessitates that programs primarily focusing on the prescription of MICE (as per the current aerobic exercise guidelines for cancer survivors) require inclusion of strategies to promote long term exercise adherence to enable clinically

meaningful changes to be achieved and that greater attention is given to avoiding periods of non-adherence to sustain elevated $\dot{V}O_2$peak levels.

Previous studies in cancer survivors have generally not found higher intensity exercise to offer superior improvements in $\dot{V}O_2$peak above moderate intensity exercise [13-16]. However, this may be due to the considerable heterogeneity amongst the high-intensity prescriptions used in these studies. High intensity interval exercise allows for increases in the duration of exercise spent at high workloads via regular recovery periods, and can be manipulated based on several variables (including work/recovery intensity, duration of interval/recovery, repetition number) [26]. It is generally thought that prescription within the high-intensity domain extends a dose-response relationship between training load (as determined by the manipulation of the above variables) and physiological adaptation due to the greater demands placed on various systems involved with high intensity exercise [26]. Considering this, the low overall training load of the short duration HIIE program reported by Schmitt et al. [16] (8x1min) compared to the present protocol (4x4min), may explain the lack of $\dot{V}O_2$peak change observed by this group, which is in contrast to the findings of the present study. Two longer duration trials that reported similar improvements between higher and lower intensity interventions gradually increased from a lower HIIE frequency ($2.week^{-1}$) [14] and intensity (intervals ranging from 50-75% $\dot{V}O_2$peak) [13] than the present trial. Additionally, Martin et al. [15] did not find any differences using a higher-intensity continuous rather than interval prescription (75-80% HR at $\dot{V}O_2$peak). However, the exercise intensity of the lower intensity group was only 9% less than the higher intensity group; this may have been insufficient to elicit differences in adaptations between the intensities. Therefore, the total load of these higher intensity prescriptions may have been insufficient, when compared to both the physiological stimulus of the parallel low-moderate intensity prescriptions and current HIIE protocol, to promote superior improvements in $\dot{V}O_2$peak. It appears that the total training volume is key to the initial acquisition of $\dot{V}O_2$peak changes, which may explain why accelerated and superior improvements were observed in the present trial.

Following accrual of changes in $\dot{V}O_2$peak in response to high-load HIIE, a tapered training frequency was investigated as a potentially effective strategy to maintain exercise-induced adaptations. Tapering of training frequency is widely used to maximise athletic performance in advance of competition, whilst also being shown to maintain improvements in $\dot{V}O_2$peak [19]. In the oncology setting, maintenance of adaptations with a decreased training frequency may have important implications for long-term exercise adherence. Despite the training frequency of the HIIE-T group being two-thirds lower than that of the HIIE group from weeks four to eight, there were no significant differences ($p \geq 0.05$) in $\dot{V}O_2$peak between the groups at any time point. The $\dot{V}O_2$peak

improvements following four weeks without training were also superior to the MICE group (HIIE, p=0.006; HIIE-T, p=0.013), indicating similar improvements between the HIIE groups. This is a particularly important finding as 'lack of time' is a commonly reported barrier to maintaining adequate physical activity levels for colorectal cancer survivors [17]. This is further supported in the present trial where the most commonly cited reason for non-participation was due to the 'time or travel commitment' (57.5%). These data suggest that improvements in $\dot{V}O_2$peak can be effectively maintained with a substantially reduced HIIE session requirement, which may help address one of the most commonly perceived barriers to physical activity for colorectal cancer survivors. This reduced training requirement may also have important implications for maintaining $\dot{V}O_2$peak during periods of additional cancer- or comorbidity-related treatments.

The present data support the design of clinical exercise programs that include an initial acute block of high load (3 sessions.week$^{-1}$) HIIE training to provide significant improvements in $\dot{V}O_2$peak followed by a maintenance period of reduced frequency of HIIE. Whilst this study only included a relatively short four-week period of tapered training, Martin et al. [15] demonstrated that clinic-based improvements in $\dot{V}O_2$peak were effectively maintained with an individualised home based program over a four-month follow up in participants who completed 8 weeks (3 sessions.week$^{-1}$) of higher intensity exercise (75-80% HR at $\dot{V}O_2$peak); participants who completed low intensity exercise (60-65% HR at $\dot{V}O_2$peak) regressed to baseline over the same timeframe. Whether or not maintenance of $\dot{V}O_2$peak with reduced training lasts beyond four weeks remains to be established.

Maintenance of $\dot{V}O_2$peak changes following the withdrawal of the training stimulus appears to be intensity specific. Both HIIE groups maintained an elevated $\dot{V}O_2$peak significantly above baseline and the MICE group after a four-week period without training, whereas results from participants in the MICE group were not different from baseline. This finding extends the work of Martin et al. [15] and shows that $\dot{V}O_2$peak improvements can be maintained, at least in the short term, even without an additional training stimulus. The mechanisms that explain this differential $\dot{V}O_2$peak maintenance between intensities are yet to be determined, however they may be specific to the primary location of adaptations [i.e. central (cardiovascular) versus peripheral (skeletal muscle)]. Future research is needed to investigate the specific improvements responsible for changes in $\dot{V}O_2$peak to better understand the mechanisms explaining the differential velocity, magnitude and maintenance of these changes between exercise intensities. Particularly if differential adaptations are indeed responsible for $\dot{V}O_2$peak changes following HIIE and MICE, a more specific understanding of tumour and treatment related

physiological impairments that underscore global reductions in $\dot{V}O_2$peak will facilitate the development of patient-specific prescriptions to optimise the benefits of exercise for colorectal cancer survivors [25].

All HIIE and MICE interventions were found to maintain lean mass. Very few trials have investigated changes in lean mass in colorectal cancer survivors following exercise. These trials have also demonstrated similar findings in lean mass following a supervised [27] and a home based [28] combined aerobic and resistance based program. A lack of improvements in lean mass in the present trial are likely explainable by the absence of anabolic-specific resistance training. In contrast, a lack of change in studies including resistance training is intriguing when considering that these populations may be more sensitive to skeletal muscle anabolism given the atrophy that can occur with colorectal cancer treatment [29, 30]. Given resistance training constitutes an important component of the exercise guidelines for cancer survivors, further research is warranted to better understand the anabolic responses to various exercise prescriptions in colorectal cancer survivors. The absence of anabolic improvements may have been further compounded by a lack of any post-exercise dietary recommendations. Recent recommendations suggest that older adults may require up to 40g.kg$^{-1}$ body weight of dietary protein (double the requirement of younger adults) following resistance-based exercise to optimise post-exercise protein synthesis [31]. Whether hypertrophic adaptations following HIIE could be facilitated with acute post-exercise protein intake remains to be determined.

HIIE significantly reduced fat mass compared to the MICE group following eight weeks of training (-0.7kg; p=0.038); these greater reductions were also maintained following withdrawal of the training intervention (-0.7kg; p=0.045). Despite only a relatively modest reduction in fat mass from baseline in the HIIE group (-1.1kg), a systematic review conducted in prostate cancer survivors has shown that exercise trials in isolation often fail to consistently promote reductions in fat mass [32]. Similarly, previous comparative trials of exercise intensity on body composition in cancer survivors have generally found no differences between interventions [13, 14, 16], further underlying the importance of the present findings. Whilst the bioenergetics of MICE promotes greater utilisation of fatty acids as a substrate for energy provision during exercise [33], HIIE has been associated with greater post-exercise fat oxidation, a factor that may explain the present findings [34, 35]. Higher intensity exercise has been shown to evoke significantly higher rates of oxygen consumption and subsequent fat oxidation compared to lower intensity exercise up to 40 minutes post-exercise in healthy young adults [36]. However other studies have shown non-significant differences in both net oxygen consumption (intra- and three hour post-exercise) [37] and 24-hour energy expenditure [38] following HIIE and MICE in healthy young males, suggesting additional factors may underscore the differences in fat mass changes between HIIE and MICE

beyond intra- and post-exercise energy expenditure. Increases in resting energy expenditure have been suggested as an additional mechanism contributing to superior reductions in fat mass following HIIE [37, 39]. In particular, resting energy expenditure has been shown to be elevated up to 19 hours following 40-minutes of moderate-vigorous aerobic exercise (~80% $HR_{peak}$) [39]. Increases in the rate of resting energy expenditure were linearly related to the intensity of exercise ($r=0.61$, $p<0.05$) suggesting that higher intensity exercise may promote greater energy expenditure via prolonged increases in resting metabolic activity after the exercise bout [39]. However, whether a similar phenomenon exists in cancer survivors and if this contributes to overall changes in fat mass following exercise at various intensities remains to be confirmed.

In the only study to also measure body composition using DXA analysis, Schmitt et al. [16] did not find any significant differences in fat mass following a three-week intervention of HIIE (8x1min; >95% $HR_{peak}$; 3 sessions.week$^{-1}$) and MICE (75min; 60% $HR_{peak}$; 2 sessions.week$^{-1}$). Despite differences in the intervention duration to the current study (3 vs. 8 weeks), the similar weekly volume of the MICE interventions (duration equivalent with current exercise oncology guidelines) suggests that the use of longer intervals (4 minutes) than used by Schmitt et al. [16] was important in promoting superior reductions in fat mass in the present trial. Therefore, increasing exercise intensity in isolation does not appear sufficient to promote superior changes in fat mass to that of moderate intensity exercise, with the duration of HIIE (and the subsequent effects on energy expenditure) appearing to also mediate this relationship. In addition to these prescriptive factors (intensity and duration), the present data also suggest a dose-response relationship between frequency of HIIE and fat mass reductions. Despite similar responses between HIIE and HIIE-T after four weeks of training (when the interventions were equivalent), only the higher exercise frequency, and therefore greater occurrence of intra- and post-exercise fat oxidation in the HIIE group led to superior reductions in fat mass compared to the MICE group following eight weeks of training and withdrawal of training. Hence, the use of a tapering strategy when prescribing HIIE for fat mass loss does not appear to offer the same effectiveness as when used for $\dot{V}O_2$peak outcomes. Therefore, if the outcome goal of an exercise intervention is to promote concurrent improvements in $\dot{V}O_2$peak as well as reductions in fat mass using HIIE, specific consideration of the exercise duration and frequency is required when determining the most appropriate prescription to optimise these improvements for colorectal cancer survivors.

Whilst this study has demonstrated important relationships between exercise intensity and cardiorespiratory fitness and body composition, there are several limitations worthy of comment. Firstly these data come from a relatively small sample of colorectal cancer survivors, and as such these preliminary findings require additional

study from larger cohorts to confirm the present results. The sample size for body composition analyses was further reduced (n=10 consecutive participants, HIIE=3, HIIE-T=5, MICE=2) due to equipment malfunction, which may have influenced the observed changes in body composition. Secondly our follow up period was relatively short (four weeks) so it is difficult to speculate on the longevity of adaptations beyond this time point. Future trials are necessary to determine the complete duration of maintenance of improvements, and whether additional adjunctive prescriptions can further bolster this maintenance. It was also evident that despite stratification by sex, there were fewer female participants randomised into the HIIE group. Regardless, the inclusion of sex as a covariate in the analysis revealed no significant effects for any of the outcomes, indicating that this imbalance following randomisation likely did not impact the outcomes. Additionally, beyond instructions to participants to maintain their usual dietary habits, it is not possible to completely exclude the possibility that alterations in dietary intake throughout the intervention may have influenced changes in fat mass or contributed to the lack of changes in lean mass.

In addition to previous data [12], the safety, high rates of completion, attendance, and adherence to the prescribed exercise intensity and duration for both HIIE and MICE programs supports the feasibility of these interventions within the supervised clinical setting. However, these data may overestimate the feasibility of HIIE and MICE programs in the community setting given the high proportion of participants that declined to participate given the travel and time commitments of this supervised clinical program. Whilst these results are encouraging based on the clinical efficacy of HIIE interventions, further research is undoubtedly required to determine the wider feasibility and subsequent efficacy and potential clinical utility of these interventions in the community setting [40].

Finally the use of $\dot{V}O_2$peak in the present trial may have underestimated the heart rate intensity prescriptions. $\dot{V}O_2$max is defined as an individual's maximal aerobic capacity, however due to difficulties in achieving this true maximum, $\dot{V}O_2$peak is often used to describe the maximal observed $\dot{V}O_2$ in a symptom limited exercise test to volitional fatigue [41]. Particularly in individuals unfamiliar with strenuous exercise, $\dot{V}O_2$peak testing to volitional fatigue may underestimate true capacity [42]. However the mean achieved RER of 1.23 in the present trial (an RER > 1.10 is recommended as an accurate and reliable measure of subject exertion [41]) during $\dot{V}O_2$peak testing tends to support the conclusion that maximal exertion was achieved in these tests. Additionally there were no significant changes in RER across the intervention (baseline = 1.22; midpoint = 1.23; endpoint = 1.23; follow-up = 1.24; p = 0.506), which suggests comparable levels of maximal exertion across the intervention and

supports the observed changes being the result of the intervention rather than due to a learning effect of exercising to volitional fatigue [41].

***Conclusions***

In conclusion, the present study found greater improvements in $\dot{V}O_2$peak and reductions in fat mass following eight weeks of thrice-weekly HIIE when compared to the current aerobic moderate-intensity exercise oncology guidelines for cancer survivors. Based on the observed superior and accelerated benefits in cardiorespiratory fitness, HIIE interventions may promote clinically meaningful improvements more efficiently and effectively than programs implementing current aerobic exercise recommendations for cancer survivors, however this remains to be confirmed with larger sample sizes. Furthermore these preliminary findings indicate that prescription of HIIE appears to offer greater programming flexibility and a decreased training burden, with improvements in cardiorespiratory fitness being accrued even following a reduced frequency of training and maintained even after four weeks of complete withdrawal of exercise training. These findings are important, as HIIE may be an effective strategy to address the physiological regressions that occur as a result of interruptions and poor adherence to long-term exercise programs. This study has provided substantial novel insight for the design and prescription of exercise-medicine programs including HIIE to promote greater health outcomes for colorectal cancer survivors.

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**Table 1:** Participant characteristics



| | All | HIIE | HIIE-T | MICE |
|---|---|---|---|---|
| n | 57 | 18 | 20 | 19 |
| Age (years) | 60.7 ± 10.9 | 60.7 ± 11.7 | 61.5 ± 10.2 | 59.8 ± 11.4 |
| Body mass (kg) | 80.6 ± 17.8 | 90.2 ± 12.5 | 73.8 ± 18.1 | 78.6 ± 18.5 |
| Body Mass Index ($kg.m^{-2}$) | 26.9 ± 4.5 | 29.8 ± 3.6 | 24.7 ± 4.5 | 26.5 ± 3.9 |
| Women [n (%)] | 25 (41.0) | 5 (27.8) | 10 (50.0) | 10 (52.6) |
| **Cancer History** | | | | |
| Colon cancer [n (%)] | 41 (71.9) | 12 (66.7) | 14 (70.0) | 15 (78.9) |
| Rectal cancer [n (%)] | 16 (28.1) | 6 (33.3) | 6 (30.0) | 4 (21.1) |
| Time since diagnosis (years) | 4.1 ± 2.5 | 3.4 ± 2.2 | 4.6 ± 2.9 | 4.3 ± 2.3 |
| Time since treatment (years) | 3.4 ± 2.6 | 2.6 ± 2.3 | 4.1 ± 3.1 | 3.3 ± 2.3 |
| **Cancer Stage [n (%)]** | | | | |
| I | 10 (17.5) | 2 (11.1) | 4 (20.0) | 4 (21.1) |
| II A | 7 (12.3) | 3 (16.7) | 1 (5.0) | 3 (15.8) |
| II B | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| III A | 5 (8.8) | 1 (5.6) | 2 (10.0) | 2 (10.5) |
| III B | 11 (19.3) | 5 (27.8) | 1 (5.0) | 5 (26.3) |
| III C | 4 (7.0) | 0 (0.0) | 4 (20.0) | 0 (0.0) |
| IV | 5 (8.8) | 3 (16.7) | 1 (5.0) | 1 (5.3) |
| Unknown | 15 (26.3 | 4 (22.2) | 7 (35.0) | 4 (21.1) |
| **Cancer Treatment [n (%)]** | | | | |
| Surgery | 20 (35.1) | 7 (38.9) | 6 (30.0) | 7 (36.8) |
| Surgery & chemotherapy | 29 (50.9) | 9 (50.0) | 11 (55.0) | 9 (47.4) |
| Surgery & radiation | 2 (3.5) | 0 (0) | 2 (10.0) | 0 (0) |
| Surgery, chemotherapy & radiation | 5 (8.8) | 2 (11.1) | 0 (0) | 3 (15.8) |
| Radiation & chemotherapy | 1 (1.8) | 0 (0) | 1 (5.0) | 0 (0) |
| **Ethnicity [n (%)]** | | | | |
| Caucasian | 54 (94.7) | 17 (94.4) | 19 (95.0) | 18 (94.7) |
| Asian | 2 (3.6) | 0 (0) | 1 (5.0) | 1 (5.3) |
| African | 1 (1.8) | 1 (5.6) | 0 (0) | 0 (0) |
| **Smoking History [n (%)]** | | | | |
| Never | 30 (52.6) | 7 (38.9) | 13 (65.0) | 10 (52.6) |
| Former | 27 (47.4) | 11 (61.1) | 7 (35.0) | 9 (47.4) |
| Current | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Education [n (%)]** | | | | |
| Primary | 4 (7.0) | 1 (5.6) | 2 (10.0) | 1 (5.3) |
| Secondary | 18 (30.6) | 8 (44.4) | 1 (5.0) | 9 (47.4) |
| Trade | 14 (24.6) | 2 (11.1) | 8 (45.0) | 3 (15.8) |
| University | 21 (36.8) | 7 (38.9) | 9 (40.0) | 6 (31.6) |
| **Marital Status [n (%)]** | | | | |
| Not-married | 1 (1.8) | 0 (0) | 1 (5.0) | 0 (0) |
| Married | 50 (87.8) | 17 (94.4) | 18 (90.0) | 15 (78.9) |
| Divorced/separated | 6 (10.6) | 1 (5.6) | 1 (5.0) | 4 (21.1) |
| **Employment [n (%)]** | | | | |
| Working | 30 (52.6) | 9 (50.0) | 9 (45.0) | 12 (63.2) |
| Retired | 27 (46.4) | 9 (50.0) | 11 (55.0) | 7 (36.8) |
| **Intervention adherence** | | | | |
| Attendance (% prescribed) | - | 99.3 ± 2.2 | 99.9 ± 0.5 | 100.0 ± 0.0 |
| Duration (% prescribed) | - | 99.8 ± 0.4 | 100.0 ± 0.0 | 100.0 ± 0.0 |
| Peak HR[a] (% $HR_{peak}$) | - | 90.6 ± 3.7 | 90.7 ± 4.3 | 71.4 ± 8.3 |

Continuous variables are presented as mean ± SD; Nominal values are presented as n (%)

[a] Average of peak HR recorded across the four HIIE intervals or at 15, 30,40 and 50 minutes during MICE

HIIE: High-intensity interval exercise; HIIE-T: High-intensity interval exercise – tapered; $HR_{peak}$: peak heart rate; MICE: Moderate-intensity continuous exercise

**Table 2:** Cardiorespiratory fitness outcome measures across the intervention

| | *0 weeks (Baseline)* | | | *4 weeks (Midpoint)* | | | *8 weeks (Endpoint)* | | | | *12 weeks (Follow up)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **$\dot{V}O_2$peak (ml·kg$^{-1}$·min$^{-1}$)** | **Mean** | **95% CI** | ***p*** | **Mean** | **95% CI** | ***p (0 vs. 4)*[a]** | **Mean** | **95% CI** | ***p (4 vs. 8)*** | ***p (0 vs. 8)*** | **Mean** | **95% CI** | ***p (8 vs. 12)*** | ***p (0 vs. 12)*** |
| HIIE (n = 16) | 23.2 | 21.8-24.5 | - | 27.4 | 26.0-28.8 | **p < 0.001** | 28.4 | 27.1-29.8 | p = 0.349 | **p < 0.001** | 27.4 | 25.9-28.8 | p = 0.349 | **p < 0.001** |
| HIIE-T (n = 16) | 23.5 | 22.2-24.8 | - | 26.8 | 25.5-28.1 | **p < 0.001** | 27.6 | 26.3-29.0 | p = 0.534 | **p < 0.001** | 26.9 | 25.5-28.2 | p = 0.534 | **p < 0.001** |
| MICE (n = 15) | 23.4 | 22.1-24.7 | - | 24.5 | 23.1-25.8 | p = 0.327 | 26.1 | 24.8-27.4 | p = 0.054 | **p < 0.001** | 24.1 | 22.6-25.5 | **p = 0.032** | p = 0.689 |
| **Between group differences** | | | **p (0)[b]** | | | **p (4)** | | | **p (8)** | | | | **p (12)** | |
| HIIE vs. MICE | -0.2 | -2.2-1.8 | p = 1.000 | 3.0 | 0.6-5.3 | **p = 0.008** | 2.3 | 0.0-4.7 | **p = 0.049** | - | 3.3 | 0.8-5.8 | **p = 0.006** | - |
| HIIE-T vs. MICE | 0.1 | -1.8-2.0 | p = 1.000 | 2.3 | 0.2-4.5 | **p = 0.030** | 1.5 | -0.6-3.7 | p = 0.210 | - | 2.8 | 0.5-5.1 | **p = 0.013** | - |
| HIIE vs. HIIE-T | -0.3 | -2.7-2.0 | p = 1.000 | 0.6 | -1.3-2.6 | p = 0.528 | 0.8 | -1.1-2.7 | p = 0.422 | - | 0.5 | -1.5-2.5 | p = 0.637 | - |

[a] Within-group comparisons between the designated weeks of the intervention
[b] Between-group comparisons at the designated week of the intervention
Linear mixed modelling analysis; fixed factors: group, time, group x time; fixed covariates: sex, baseline variable score; random factors: participants
Data from six participants were excluded from $\dot{V}O_2$peak analysis due to inabilities in completing a valid test (HIIE = 1; HIIE-T = 2; MICE = 2). Additionally, data from one participant in the HIIE-T group was excluded as an outlier, as the participant was substantially fitter than the average of the cohort ($\dot{V}O_2$peak = 53.9 ml.kg$^{-1}$.min$^{-1}$, cohort mean = 23.3 ml.kg$^{-1}$.min$^{-1}$).
HIIE: High intensity interval exercise; HIIE-T: High intensity interval exercise – tapered; MICE: moderate intensity continuous exercise; $\dot{V}O_2$peak: peak oxygen uptake

**Table 3:** Body composition outcome measures across the intervention

| | *0 weeks (Baseline)* | | | *4 weeks (Midpoint)* | | | *8 weeks (Endpoint)* | | | | *12 weeks (Follow up)* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Lean mass (kg)** | **Mean** | **95% CI** | ***p*** | **Mean** | **95% CI** | ***p (0 vs. 4)*** [a] | **Mean** | **95% CI** | ***p (4 vs. 8)*** | ***p (0 vs. 8)*** | **Mean** | **95% CI** | ***p (8 vs. 12)*** | ***p (0 vs. 12)*** |
| HIIE (n = 14) | 45.1 | 44.6-45.6 | - | 45.7 | 45.2-46.2 | p = 0.075 | 45.6 | 45.1-46.1 | p = 1.000 | p = 0.141 | 45.6 | 45.0-46.1 | p = 1.000 | p = 0.269 |
| HIIE-T (n = 14) | 45.1 | 44.6-45.5 | - | 45.5 | 45.0-46.0 | p = 0.665 | 45.5 | 45.0-46.0 | p = 1.000 | p = 0.682 | 45.4 | 44.9-46.0 | p = 1.000 | p = 0.730 |
| MICE (n = 15) | 45.0 | 44.6-45.5 | - | 45.4 | 44.9-45.9 | p = 0.522 | 45.6 | 45.1-46.1 | p = 0.841 | p = 0.157 | 45.8 | 45.3-46.3 | p = 0.841 | **p = 0.027** |
| **Between group differences** | | | **p (0)** [b] | | | **p (4)** | | | **p (8)** | | | | **p (12)** | |
| HIIE vs. MICE | 0.0 | -0.8-0.9 | p = 1.000 | 0.3 | -0.5-1.2 | p = 1.000 | 0.1 | -0.7-0.8 | p = 1.000 | - | -0.2 | -1.1-0.6 | p = 1.000 | - |
| HIIE-T vs. MICE | 0.0 | -0.6-0.7 | p = 1.000 | 0.1 | -0.6-0.8 | p = 1.000 | -0.1 | -0.9-0.6 | p = 1.000 | - | -0.4 | -1.3-0.5 | p = 0.910 | - |
| HIIE vs. HIIE-T | 0.0 | -0.7-0.7 | p = 1.000 | 0.2 | -0.6-1.1 | p = 1.000 | 0.2 | -0.7-1.1 | p = 1.000 | - | 0.1 | -0.7-0.1 | p = 0.938 | - |
| **Fat mass (kg)** | **Mean** | **95% CI** | ***p*** | **Mean** | **95% CI** | ***p (0 vs. 4)*** [a] | **Mean** | **95% CI** | ***p (4 vs. 8)*** | ***p (0 vs. 8)*** | **Mean** | **95% CI** | ***p (8 vs. 12)*** | ***p (0 vs. 12)*** |
| HIIE (n = 14) | 26.4 | 26.0-26.8 | - | 25.7 | 25.3-26.1 | **p = 0.006** | 25.3 | 24.9-25.7 | p = 0.138 | **p < 0.001** | 25.4 | 25.0-25.8 | p = 0.554 | **p < 0.001** |
| HIIE-T (n = 14) | 26.3 | 25.9-26.7 | - | 25.7 | 25.3-26.1 | **p = 0.021** | 25.6 | 25.2-26.0 | p = 1.000 | **p = 0.004** | 25.5 | 25.1-26.0 | p = 1.000 | **p = 0.004** |
| MICE (n = 15) | 26.3 | 25.9-26.6 | - | 26.1 | 25.7-26.5 | p = 1.000 | 26.0 | 25.6-26.3 | p = 1.000 | p = 0.994 | 26.1 | 25.7-26.5 | p = 1.000 | p = 1.000 |
| **Between group differences** | | | **p (0)** [b] | | | **p (4)** | | | **p (8)** | | | | **p (12)** | |
| HIIE vs. MICE | 0.1 | -0.5-0.8 | p = 1.000 | -0.39 | -1.0-0.3 | p = 0.456 | -0.7 | -1.4-0.0 | **p = 0.038** | - | -0.7 | -1.4-0.0 | **p = 0.045** | - |
| HIIE-T vs. MICE | 0.1 | -0.5-0.6 | p = 1.000 | -0.37 | -1.0-0.3 | p = 0.456 | -0.4 | -1.0-0.2 | p = 0.324 | - | -0.6 | -1.3-0.1 | p = 0.082 | - |
| HIIE vs. HIIE-T | 0.1 | -0.5-0.7 | p = 1.000 | -0.02 | -0.6-0.6 | p = 0.948 | -0.3 | -0.9-0.2 | p = 0.324 | - | -0.1 | -0.7-0.5 | p = 0.725 | - |

[a] Within-group comparisons between the designated weeks of the intervention

[b] Between-group comparisons at the designated week of the intervention

Linear mixed modelling analysis; fixed factors: group, time, group x time; fixed covariates: sex, baseline variable score; random factors: participants

Data from 10 consecutive participants (HIIE = 3, HIIE-T = 5, MICE = 2) were unavailable for analysis.

HIIE: High intensity interval exercise; HIE-T: High intensity interval exercise - tapered MICE: moderate intensity continuous exercise

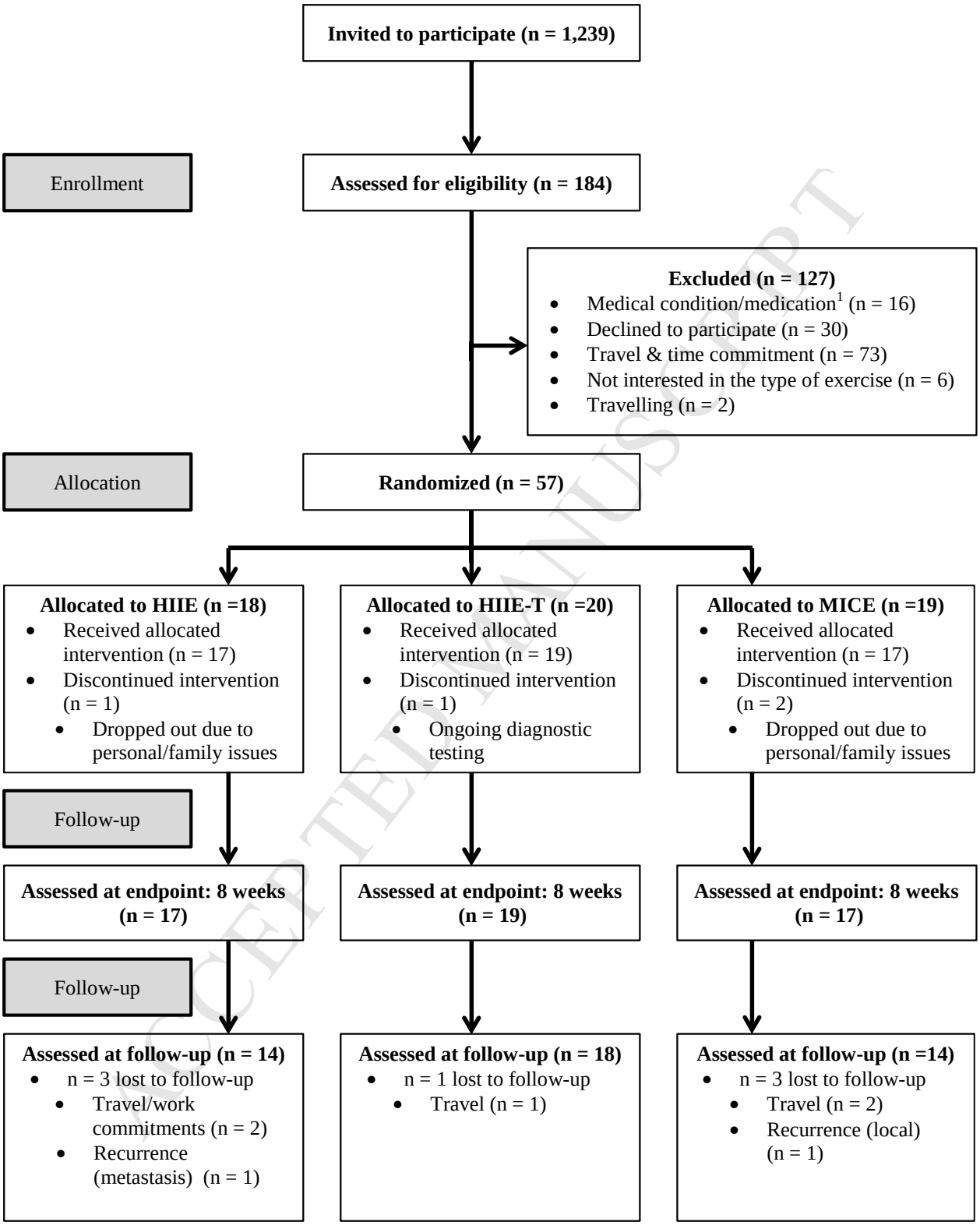


**Figure 1:** CONSORT diagram illustrating participant flow through the intervention.
[1] As part of specified exclusion criteria requiring screening on initial contact, other reasons were participant-decided exclusions.
HIIE: High intensity interval exercise; HIIE-T: High intensity interval exercise – tapered; MICE: moderate intensity continuous exercise.