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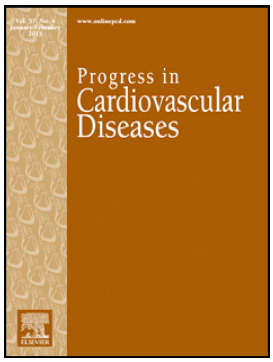

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Effect of High Intensity Interval Training on Cardiac Function in Children with Obesity: a Randomised Controlled Trial

Short title: HIIT and Cardiac Function in Obese Children

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ABSTRACT

Background: High intensity interval training (HIIT) confers superior cardiovascular health benefits to moderate intensity continuous training (MICT) in adults and may be efficacious for improving diminished cardiac function in obese children. The aim of this study was to compare the effects of HIIT, MICT and nutrition advice interventions on resting left ventricular (LV) peak systolic tissue velocity (S') in obese children.

Methods: Ninety-nine obese children were randomised into one of three 12-week interventions, 1) HIIT [n=33, 4 x 4 min bouts at 85–95% maximum heart rate (HR_{max}), 3 times/week] and nutrition advice, 2) MICT [n=32, 44 mins at 60–70% HR_{max}, 3 times/week] and nutrition advice, and 3) nutrition advice only (nutrition) [n=34].

Results: Twelve weeks of HIIT and MICT were equally efficacious, but superior to nutrition, for normalising resting LV S' in children with obesity (estimated mean difference 1.0cm/s, 95% confidence interval 0.5 to 1.6cm/s, P<0.001; estimated mean difference 0.7cm/s, 95% confidence interval 0.2 to 1.3cm/s, P=0.010, respectively).

Conclusions: Twelve weeks of HIIT and MICT were superior to nutrition advice only for improving resting LV systolic function in obese children.

Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT01991106

ABBREVIATIONS

a’	Peak late diastolic tissue velocity
BMI	Body mass index
CRF	Cardiorespiratory fitness
CV	Cardiovascular
CVD	Cardiovascular disease
e’	Peak early diastolic tissue velocity
EF	Ejection fraction
FMD	Flow mediated dilation
GLS	Global longitudinal strain
HIIT	High intensity interval training
HR_{max}	Maximum heart rate
LMM	Linear mixed model
LV	Left ventricle
MICT	Moderate intensity continuous training
NTNU	Norwegian University of Science and Technology
REML	Restricted maximum likelihood
RV	Right ventricle
S’	Peak systolic tissue velocity
SD	Standard deviation
SR	Strain rate
UQ	The University of Queensland
$\dot{V}max_{LVOT}$	Maximal velocity in left ventricular outflow tract
$\dot{V}O_{2peak}$	Peak oxygen uptake
W	Watts

Pediatric obesity is associated with increased all-cause and cardiovascular (CV) mortality [1,2], independent of adult adiposity [3]. Resting echocardiographic studies show significant systolic and diastolic alterations in cardiac function among children with obesity including lower left ventricular (LV) peak systolic tissue velocity (S'), global longitudinal strain (GLS) and strain rate (SR) when compared to their healthy-weight counterparts [4-9]. Alterations in cardiac function may be unmasked earlier and be more pronounced during peak exercise [5] which highlights the importance of maximal exercise testing in this population [10]. Prognostically, S' is a strong and independent predictor of event-free survival in adults with acute coronary syndrome, is robust and can be easily obtained during rest and exercise [11]. Subclinical impairments in cardiac function may be accompanied by endothelial dysfunction as assessed by brachial artery flow-mediated dilation [12-14], supporting the notion that children with obesity are at increased risk for development of CV disease (CVD) when compared to children with a healthy weight.

While regular exercise may normalise subclinical reductions in CV function observed in obese children [5,9,15], there is often poor adherence to current physical activity guidelines among all children[16]. High intensity interval training (HIIT) is highly efficacious for ameliorating CV and cardiometabolic outcomes in adults with chronic disease [17-22] and children with obesity [23] compared to moderate intensity continuous training (MICT) or standard care. However, it is currently unknown whether HIIT can normalise subclinical reductions in CV function among obese children.

Therefore, the aim of this investigation was to compare the effect of twelve weeks of HIIT, MICT and nutrition advice on resting systolic cardiac function (LV S') in children with obesity. We hypothesised that HIIT would be more efficacious than MICT or nutrition advice only for improving systolic cardiac function (LV S') at rest. In addition to the primary outcome, we aimed to compare the effect of the three interventions on LV and right

ventricular (RV) resting diastolic cardiac function (tissue Doppler velocities), GLS and SR during rest, peak exercise and recovery.

METHODS

Ninety-nine children with obesity, aged 7-16 years old (BMI ≥ percentile curves that pass through 30kg/m^2 at age 18) [24,25] were recruited into a multicenter randomised controlled trial (Clinicaltrials.gov NCT01991106) at The University of Queensland (UQ), Brisbane, Australia and The Norwegian University of Science and Technology (NTNU), Trondheim, Norway between March 2012 and February 2017. In the same time period, 100 healthy-weight children, aged 7-16 years old (BMI percentile curves that pass through 18kg/m^2 – 25kg/m^2 at age 18) [24,25] were assessed for comparative purposes but did not partake in the intervention. Parents or legal guardians of participants approved consent while participants provided written assent prior to participation. Participants were excluded if they presented with any of the following: hypertension, history of evidence of cardiac abnormalities, diabetes, smoking, or orthopaedic/neurological limitations that impacted their ability to exercise. Participants were not offered incentives for participating in the trial. Following baseline assessments, participants were randomly assigned 1:1:1 between three interventions and were stratified by age and sex. Allocation was performed by a web-based randomisation system developed and administered by Unit of Applied Clinical Research, The Faculty of Medicine and Health Sciences, NTNU, Norway and was fully concealed until the intervention was assigned. Detailed ethical approval, eligibility criteria, recruitment processes, randomisation procedures and study outcomes are outlined in the protocol [26].

Participants were assessed for the following outcomes, (1) cardiac function and structure, (2) vascular function, and (3) cardiorespiratory fitness (CRF), in research laboratories at NTNU and UQ, and in hospital outpatient settings (St. Olav's Hospital, Trondheim and the Wesley Hospital, Brisbane) at baseline and following the 12-week

intervention. Identical equipment and methodologies were used for each individual at each assessment. However, there were methodological differences between study centers for assessment of vascular function, which have been outlined in Supplemental Methods.

Resting Echocardiography

A full resting echocardiogram was conducted with a Vivid 7/E9/E95 ultrasound machine (GE Vingmed Ultrasound, Horten, Norway) using a phased-array transducer (GE M3S/M4S, 1.5 – 4 MHz). Three cine loops from the three standard apical planes (four-chamber, two-chamber and five-chamber), and the parasternal long axis were recorded in grey scale harmonic mode and tissue Doppler mode simultaneously. LV and RV systolic and diastolic function was assessed through standard Doppler echocardiographic indices (Supplemental Methods). Myocardial deformation analysis (speckle tracking echocardiography) was used to determined LV and right RV GLS and SR and is detailed in Supplemental Methods.

Exercise Stress Echocardiography

Following the resting echocardiogram, individuals exercised on a stationary cycle ergometer and apical 4-chamber and 2-chamber images in standard B-mode and B-mode with colour tissue Doppler were acquired in an upright, seated position during peak exercise for quantification of LV S', e' and A' (Supplemental Methods). The cycling protocol started at an intensity of 25W and participants were subjected to 25W increments every three minutes until they attained their maximum heart rate or were no longer able to maintain a constant cadence. Apical 4-chamber and 2-chamber images in B-mode with colour tissue Doppler were acquired following e'-A' separation for quantification of S', e' and A' during recovery. Time to e'-A' separation was also recorded.

EchoPAC (Version 112, GE Medical Systems, Milwaukee, WI, USA) was used for all echocardiographic analysis by a trained investigator and cardiologist who were blinded to the group allocation of the participants.

Vascular Function

Endothelial function of the brachial artery was measured via flow mediated dilation (FMD) using high-resolution vascular ultrasound (12–14MHz ultrasound- Doppler probe, Vivid 7 system/Vivid I system; GE Vingmed Ultrasound AS, Horten, Norway) in accordance with current methodological guidelines [27] and is further outlined in Supplemental Methods.

Cardiorespiratory Fitness

Participants completed a treadmill ramp protocol with respiratory gas analysis (Metamax 3B, Cortex Biophysik GmbH, Leipzig, Germany or Jaeger Oxycon Pro, CareFusion, Hoechberg, Germany) and a facemask system (Hans Rudolph, KS, USA) (Supplemental Methods). $\dot{V}O_{2peak}$ was calculated as the average of the two highest 30-second values attained.

Interventions

Obese children were randomised into one of three groups (HIIT, MICT or nutrition alone) and all interventions were conducted continuously. The exercise interventions (HIIT and MICT) were designed to be isocaloric and required participants to train three times per week for 12 weeks. A minimum of two sessions were supervised by an exercise physiologist each week, while the third session could be unsupervised. Exercise protocols have been outlined in **Figure 1** and are detailed in the study protocol [26]. All groups received between four and six 20–30 minute nutrition consultations with a dietitian. Individual nutrition sessions were location-specific and were based on current Norwegian [28] and Australian [29]

eating guidelines, specifically focusing on healthy food choices, portion sizes and regular meal times.

Statistical Analysis

For calculation of sample size, the clinically meaningful difference in peak systolic tissue velocity was set to 1cm/s with a standard deviation of 0.9cm/s [11] (power=0.80, alpha=0.05) and after accounting for 15% dropout, 105 participants were required to enter the randomised controlled trial. The sample size calculation is further detailed in the study protocol [26].

Data are presented as mean (SD) if continuous and normally distributed, and medians (interquartile ranges) or counts (percentages) if non-normally distributed or categorical. A linear regression was used to estimate differences between obese and healthy-weight children at baseline, accounting for age, sex and center. Differences between the interventions were analysed using linear mixed models (LMMs), adjusting for age, sex and center, and allowing for a heterogeneous residual variance between centers. A subject-specific random intercept was used to account for within-participant correlations. The baseline means were restricted to be equal for all three interventions as participants were randomly allocated to a group. Likelihood ratio tests were used to determine overall effects and the final model was fitted using restricted maximum likelihood (REML). Between-group pairwise comparisons were carried out using Wald tests. Normality of raw data and residuals from the LMMs or linear regressions were assessed through visual examination of normal quantile-quantile plots and histograms and results from the Shapiro-Wilk test or Anderson-Darling test. Where outcomes of interest were transformed to satisfy model assumptions, the model parameter estimates are presented in the natural logarithmic (ln) transformed scale.

An intention-to-treat (HIIT=33; MICT=32; nutrition=34) and per protocol analysis (HIIT=17; MICT=24; nutrition=21) was conducted for the LMM. All available data were

included in the intention-to-treat analysis, since the method of estimation for the LMM handles missing data. We assumed that data were missing at random, in which case the method produces unbiased estimates. For the per protocol analysis, participants were required to complete ≥80% of the exercise and/or nutrition sessions. Trial completion was calculated as (total number of sessions attended/total number of sessions available) x 100. SPSS Statistics (Version 24.0, IBM, Armonk, NY, USA) and the R Statistical Package (RStudio Team, Boston, MA, USA) were used to conduct statistical analyses. P values <0.05 were considered statistically significant. As there was only one primary outcome and the results of secondary outcomes were exploratory and interpreted as hypothesis generating, no formal adjustment for multiple testing was included.

RESULTS

A CONSORT diagram (**Figure 2**) summarises participant flow through each stage of the trial and outlines reasons for participant drop out. All available data were included in the intention-to-treat analysis and have been presented in a tabular format. Out of 99 participants who were randomised (NTNU = 68; UQ = 31), 62 participants (63%) successfully completed the trial and were included in per protocol analyses (NTNU=42; UQ = 20). Outcomes of per protocol analyses are only presented in-text when statistical significance of the intervention effect differed between per protocol and intention-to-treat analyses.

Obese and Healthy-Weight Children

A summary of baseline characteristics and comparison of (CV) outcomes for obese and healthy-weight children are presented in **Supplemental Table 1.** There were no differences in age, sex or Tanner stage of puberty between the populations (obese: 12.0 (2.3 years), 53 [53.5%] female, Tanner stage 3 [2–4]; healthy-weight: 11.5 (2.4 years), 50 [51.0%] female, Tanner stage 2 [1–3]). Obese children showed lower LV and RV systolic and

diastolic function at rest when compared to healthy-weight children including significantly lower resting LV peak systolic tissue velocity (-1.7cm/s, 95% CI -2.0 to -1.3cm/s, P<0.001).

Intervention Effects in Obese Children

There were no differences in age, sex and Tanner stage of puberty between intervention groups (HIIT: 12.4 (1.9 years), 17 [51.5%] female, Tanner stage 3 [2– 4]; MICT: 11.9 (2.4 years), 17 [53.1%] female, Tanner stage 2 [1–4]; nutrition: 11.8 (2.4 years), 19 [55.9%] female, Tanner stage 3 [1–4]). Exercise training data are presented in **Table 1.** There were no adverse events over the study duration.

A summary of CV outcomes at baseline and post intervention is presented for each group (**Table 2 and Supplemental Table 2). Table 3 and Supplemental Table 3** present the estimated between-group intervention effects for all outcomes. Linear mixed models were also fitted to include an interaction effect between center and intervention. However, this interaction effect was only significant for five outcome variables. In light of multiple testing, and for ease of interpretation and generalizability of findings, the results presented are for models without this interaction effect, but were adjusted for center by a main effect. Model parameters were also adjusted for age and sex effects on outcomes of interest (**Table 3**).

Resting Cardiac Function

Twelve weeks of HIIT and MICT significantly improved systolic cardiac function (LV S') at rest compared to the nutrition only group (1.0cm/s, 95% CI 0.5 to 1.6cm/s, P<0.001; 0.7cm/s, 95% CI 0.2 to 1.3cm/s, P=0.010, respectively) (**Figure 3 A & C**). There were no significant differences between the HIIT and MICT interventions for changes in LV S'. Intervention effects were noted for global cardiac function with HIIT demonstrating superior increases in ejection fraction (EF; 4.0 percent point (pp), 95% CI 0.1 to 8.0pp, P=0.045) and stroke volume index (6.8mL/m^2, 95% CI 2.7 to 10.9mL/m^2, P=0.001) when compared to MICT. The

benefits of HIIT and MICT compared to the nutrition only intervention appeared to extend to resting RV function with increases noted in e', GLS and SR (**Table 3**).

In addition, HIIT improved RV e' (2.1cm/s, 95% CI 0.5 to 3.6cm/s, P=0.009) and GLS (-3.0pp, -0.5 to -5.5pp, P=0.020) compared to twelve weeks of MICT.

Peak Exercise and Recovery Cardiac Function

Pairwise comparisons for LV S', $\dot{V}max_{LVOT}$, and stroke volume index at peak exercise revealed that while there were no differences between HIIT and MICT interventions, the exercise interventions were superior to nutrition advice only for eliciting improvements in these outcomes (**Table 3, Figure 3 B & D**). Importantly, the estimated mean differences between the exercise and nutrition groups for peak exercising LV S' were clinically significant [11]. The exercise interventions increased recovery systolic cardiac function (LV S') compared to the nutrition only intervention while the HIIT group exhibited greater improvements in recovery diastolic cardiac function (LV e') compared to the nutrition only group (**Supplemental Table 3**).

Vascular Function and Cardiorespiratory Fitness

Vascular function assessed through brachial FMD improved in the nutrition only group compared to the HIIT (4.2pp, 95% CI 1.2 to 7.2pp, P=0.005) and MICT (3.3pp, 0.3 to 6.3pp, P=0.033) interventions. Given this is in stark contrast with previous research, we recognise it may be a spurious finding resulting from multiple testing. Per protocol analysis revealed a clinically significant difference in CRF between the HIIT and MICT groups (3.6mL/kg/min, 95% CI 1.1 to 6.0mL/kg/min, P=0.004).

DISCUSSION

Pediatric obesity leads to detrimental CV changes and impacts future CVD risk and premature mortality [1,2]. To the best of our knowledge, this is the first randomised controlled trial to compare the efficacy of HIIT and MICT on cardiac function in obese children. Our

novel findings show that twelve weeks of HIIT and MICT were superior to nutrition advice only for improving resting systolic cardiac function (LV S') in pediatric obesity. Importantly, both exercise interventions normalised LV S' in obese children compared to their healthy weight counterparts (post HIIT versus healthy-weight, P=0.38; post MICT versus healthy-weight, P=0.19). The complex mechanics of the heart are best represented by several outcome measures and HIIT conferred significantly greater improvements in global cardiac function, and RV myocardial contractility compared to MICT and nutrition advice only. Secondly, results suggested that the favourable effects of the exercise training interventions compared to the nutrition intervention extended to peak exercising cardiac function in this population. Together, these findings highlight the importance of regular exercise, potentially of a higher intensity, to ameliorate cardiac health in children with obesity.

Although we hypothesised that HIIT would be more effective than MICT for improving the primary outcome, resting systolic cardiac function (LV S'), both exercise interventions were equally efficacious and superior to the nutrition only intervention. Still, our findings suggest that HIIT was a more potent stimulus for improving global cardiac function and myocardial contractility than MICT. This is consistent with evidence from adults with chronic disease [18,19,30-32] and animal models [33-35]. Wisloff et al. (2007) showed that twelve weeks of HIIT was superior to MICT and standard care for improving EF (10pp or 35% increase, P<0.020) in patients with stable post infarction heart failure [18]. While the increase in EF following HIIT in our study was smaller than previously noted in clinical adult populations (4.3pp or 7.5% increase, P=0.004), we note that HIIT normalised EF compared to the healthy-weight controls (post HIIT EF 61.8% versus healthy weight EF 62.5%, P=0.58). This outcome is complemented by a significant increase in stroke volume and stroke volume index noted in our study and previous work [5,18,19,32]. Importantly, improvements in tissue Doppler velocities bear prognostic significance. Westholm et al. (2013) illustrated that

a 0.9cm/s reduction in systolic cardiac function (LV S') was associated with all-cause mortality, myocardial infarction or rehospitalisation for heart failure in acute coronary syndrome patients [11]. While this observation may appear irrelevant to children with obesity, this population exhibits markedly diminished cardiac function and significant alterations in cardiac structure, when compared to healthy-weight counterparts. Given the reasonable likelihood that obese children will become obese adults [36], our data support a role for exercise interventions to ameliorate cardiac function early in childhood and adolescence to prevent CVD later in adult life.

Our study indicates that significant improvements in RV systolic (GLS) and diastolic (e') function can be attained following twelve weeks of HIIT compared to MICT and nutrition only. Pediatric obesity is associated with subclinical premature reductions in RV systolic and diastolic function as demonstrated by this study and earlier findings [8]. These alterations may be resolved through a diet-induced weight reduction in obese children [37]. To our knowledge, this is the first multidisciplinary lifestyle intervention that incorporates HIIT, to potentially restore systolic and diastolic RV function in children with obesity.

While we hypothesised that HIIT would be the most beneficial intervention for eliciting increases in peak exercise cardiac function, our findings showed no differences between the exercise interventions (HIIT and MICT). As expected, the HIIT and MICT groups exhibited superior systolic function during peak exercise following the interventions (LV S', peak ejection velocity in the LV outflow tract, indexed-stroke volume) in comparison to the nutrition only group. To our knowledge, pilot work by our group is the only other study to report peak exercise echocardiography outcomes showing significant increases in S' and peak ejection velocity following a HIIT intervention [5]. The extent to which peak exercising cardiac function improves as a consequence of short-term exercise training is currently unclear and may be partially attributed to the accuracy of assessment. Further research is

warranted in pediatric and adult populations alike to contribute to the paucity of evidence exploring this outcome.

This is the first study to illustrate the efficacy of HIIT and MICT on cardiac function in children with obesity to date. Future studies should attempt to replicate these results in larger and more diverse cohorts. We acknowledge that the vascular function results are limited methodological discrepancies between the study centres which may explain why our finding is contrary to the results of a recent meta-analysis in children with obesity [38]. Furthermore, peak oxygen uptake and exercising cardiac function were not assessed simultaneously; peak heart rate was significantly lower (30 beats/min) during the exercise echocardiography assessments than during the CRF assessment to permit acquisition of clear images. This limits our ability to make precise mechanistic conclusions. It also unclear whether the superior effect of HIIT on global cardiac function and CRF in our study, is due to increased intensity or the presence of intermittent efforts when compared to MICT [39]. Recent evidence suggests that moderate intensity interval training may provide similar benefits with regards to metabolic health in obese adolescent females [40], and fat oxidation in obese men [41]. While this type of training may be particularly relevant in high-risk clinical populations, current evidence regarding the benefits of moderate intensity interval training, particularly on CV function, remains limited. Finally, it is important to consider the retention and adherence of participants in the exercise program. While we hypothesised that children would express increased enjoyment during HIIT as the stop-start nature of this exercise prescription closely reflected childhood play, we noted marginally greater attrition in the HIIT group (30%) compared to the MICT (25%) and nutrition advice only (21%) interventions, with 25% of children dropping out of the overall intervention. To date, program completion is the only available outcome assessing ‘enjoyment’ or acceptability of HIIT and MICT interventions in pediatric obesity. It is pertinent that future research assesses enjoyment using validated scales

or questionnaire as without enjoyment, individuals are unlikely to adhere to exercise, particularly in an unsupervised setting. Furthermore, although a 'lack of time, interest and motivation' were the most commonly stated reasons for attrition, these opinions likely reflect the entire family, as children were strongly dependent on their parents particularly for transportation to and from the study centres. In light of this, we believe that family-based interventions may be more successful with regards to retention and adherence however current evidence remains limited.

In conclusion, twelve weeks of HIIT and MICT improved resting systolic cardiac function (LV S') in children with obesity to similar levels seen in healthy-weight children. Moreover, it appears that HIIT ameliorated other outcomes of resting and peak exercise cardiac function in children with obesity. These findings advocate for structured exercise programs, including HIIT to improve CV health outcomes in pediatric obesity.

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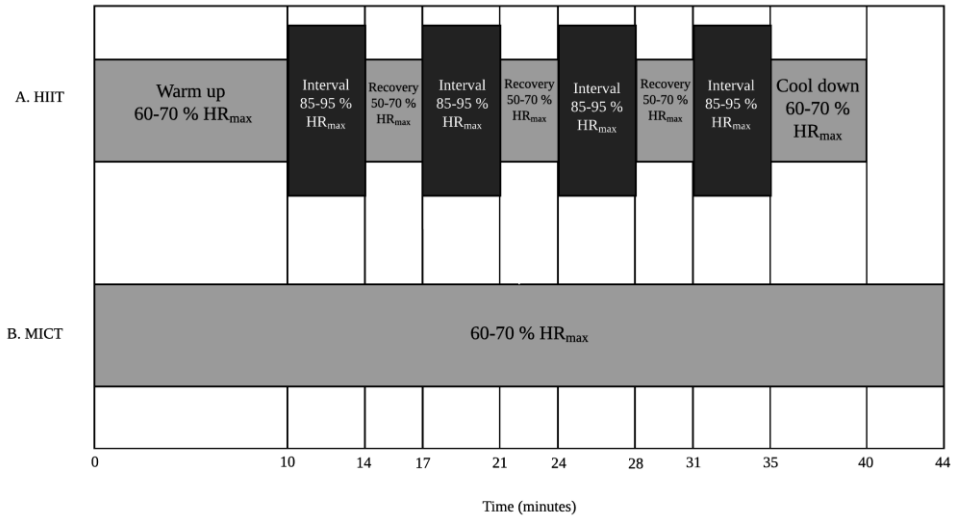
FIGURE LEGENDS

Figure 1. Exercise training protocols. Schematic representation detailing time and intensity of A. HIIT and B. MICT sessions

Figure 2. CONSORT flow chart. Illustration detailing the number of patients enrolled, randomised and assessed at each time point.

Figure 3. Effect of the interventions on peak systolic tissue velocity at rest (A, C) and peak systolic tissue velocity at peak exercise (B, D). A. and B. illustrate the mean (horizontal bar) and individual (circles) change scores for each intervention group while C. and D. show between-group comparisons (estimated mean difference and 95% confidence intervals). * Significant intervention effect (P = 0.001 [A] and P = 0.040 [B]).

FIGURES



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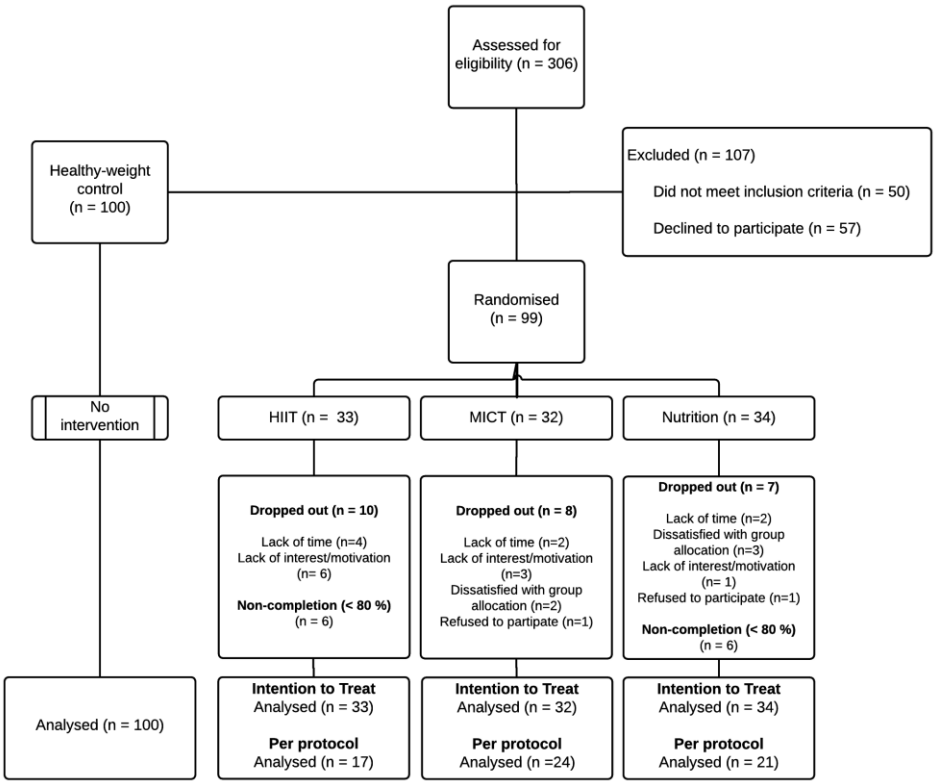

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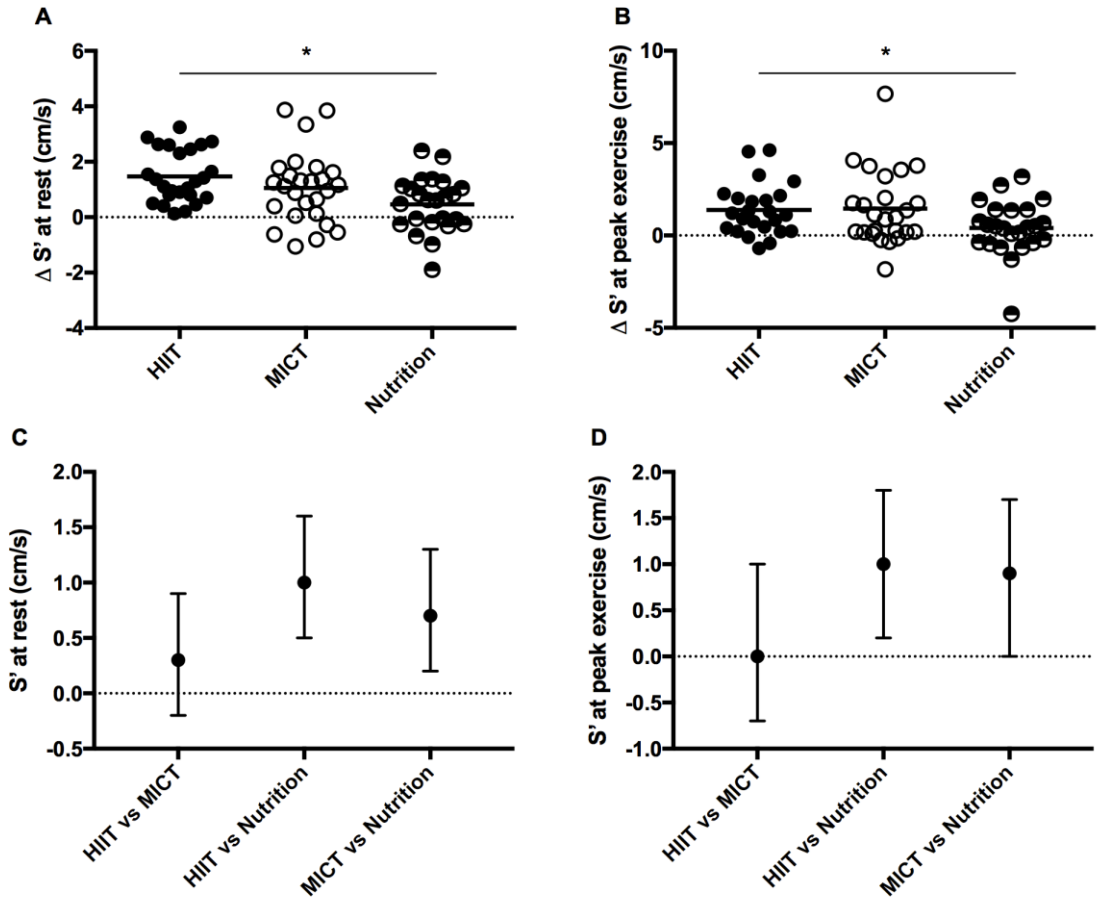

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* Significant intervention effect (P = 0.001 [A] and P = 0.040 [B]).

Table 1. Exercise training data for the two training arms

Average/session month	**1**	**2**	**3**	**Average**
HIIT (n = 17)				
Average HR (bpm)	174 (13)	175 (13)	174 (10)	173 (10)
Intensity (HR_{max}%)	90 (4)	91 (4)	91 (3)	91 (3)
Duration (min)	40 (0)	40 (0)	40 (0)	40 (0)
Attendance (%)	74 (23)	68 (30)	63 (34)	68 (27)
MICT (n = 24)				
Average HR (bpm)	137 (9)	136 (9)	138 (11)	132 (9)
Intensity (HR_{max}%)	72 (5)	72 (5)	73 (6)	72 (5)
Duration (min)	44 (0)	44 (0)	44 (0)	44 (0)
Attendance (%)	66 (25)	60 (31)	41 (35)	56 (27)

HIIT, high intensity interval training; MICT, moderate intensity interval training; HR, heart rate. Mean (SD) shown for participants who completed the intervention (per protocol analysis)

Table 2. Baseline and post intervention data for cardiac function during rest and peak exercise

	HIIT				MICT				Nutrition			
	Baseline		Post		Baseline		Post		Baseline		Post	
Variable	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**
LV function at rest												
S' (cm/s)	*33*	8.6 (1.5)	*25*	10.1 (1.6)	*32*	8.8 (1.3)	*26*	9.8 (1.7)	*34*	8.4 (0.9)	*24*	8.8 (1.1)
e' (cm/s)	*33*	14.9 (2.2)	*25*	17.1 (2.4)	*32*	15.3 (2.2)	*26*	16.2 (2.3)	*34*	15.0 (2.3)	*24*	15.4 (2.7)
A' (cm/s)	*32*	6.9 (1.5)	*25*	7.3 (1.3)	*32*	7.0 (1.3)	*26*	7.2 (1.4)	*34*	7.1 (0.8)	*24*	7.1 (0.9)
GLS (%)	*33*	-17.3 (3.0)	*23*	-18.9 (2.1)	*32*	-17.3 (3.0)	*26*	-18.1 (2.7)	*33*	-16.7 (3.0)	*22*	-16.8 (2.6)
SR (s^{-1})	*33*	-0.9 (0.2)	*23*	-1.0 (0.1)	*32*	-0.9 (0.1)	*26*	-1.0 (0.1)	*33*	-0.9 (0.2)	*21*	-0.9 (0.1)
LVEDVi (mL/m^2)	*33*	64.6 (18.4)	*25*	74.4 (17.9)	*32*	68.2 (17.8)	*26*	68.4 (15.5)	*34*	61.2 (20.9)	*27*	64.3 (20.4)
LVESVi (mL/m^2)	*33*	27.6 (10.7)	*25*	30.4 (10.9)	*32*	27.1 (7.1)	*26*	28.8 (7.4)	*34*	27.0 (9.1)_	*27*	28.5 (8.9)
EF (%)	*33*	57.5 (8.7)	*25*	61.8 (6.8)	*32*	58.4 (8.0)	*26*	58.3 (7.0)	*34*	55.0 (7.7)	*27*	54.4 (6.3)
SVi (mL/m^2)	*32*	40.2 (8.6)	*25*	46.3 (9.6)	*32*	40.5 (9.2)	*25*	39.0 (8.5)	*34*	39.0 (9.6)	*24*	38.6 (11.0)
CI ($L/min/m^2$)	*32*	3.0 (0.5)	*22*	2.9 (0.6)	*32*	3.2 (0.8)	*25*	2.9 (0.7)	*34*	3.0 (0.7)	*24*	2.8 (0.8)

RV function at rest												
S' (cm/s)	*32*	13.1 (2.0)	*24*	14.9 (2.3)	*32*	13.5 (2.2)	*23*	14.3 (2.2)	*34*	12.7 (2.1)	*24*	13.5 (2.5)
e' (cm/s)	*32*	15.1 (2.9)	*24*	17.1 (3.0)	*32*	14.9 (2.8)	*23*	15.0 (3.2)	*34*	14.5 (2.9)	*24*	14.6 (2.2)
A' (cm/s)	*32*	9.2 (2.5)	*24*	9.8 (2.5)	*32*	8.6 (2.5)	*23*	9.3 (2.6)	*34*	10.0 (3.2)	*24*	9.3 (2.3)
GLS (%)	*31*	-20.4 (4.6)	*21*	-25.6 (5.2)	*30*	-19.6 (5.9)	*23*	-21.4 (6.6)	*28*	-21.1 (3.8)	*21*	-22.0 (5.5)
SR (s^{-1})	*31*	-1.2 (0.3)	*23*	-1.5 (0.5)	*30*	-1.2 (0.5)	*23*	-1.5 (0.6)	*31*	-1.2 (0.3)	*21*	-1.2 (0.6)
LV function during peak exercise												
S' (cm/s)	*32*	13.4 (2.0)	*25*	14.7 (1.3)	*31*	13.0 (2.3)	*26*	14.2 (1.5)	*33*	12.8 (2.3)	*25*	13.5 (1.5)
e' (cm/s)	*32*	13.9 (1.7)	*25*	14.1 (1.6)	*31*	13.4 (2.3)	*26*	13.9 (1.6)	*33*	13.7 (2.2)	*25*	13.6 (2.0)
$\dot{V}max_{LVOT}$ (m/s)	*30*	1.5 (0.3)	*21*	1.7 (0.2)	*32*	1.5 (0.4)	*24*	1.6 (0.3)	*32*	1.5 (0.2)	*24*	1.4 (0.3)
SVi (mL/m^2)	*30*	35.2 (9.0)	*20*	44.2 (9.7)	*32*	40.7 (19.0)	*23*	40.1 (10.3)	*32*	40.4 (9.4)	*23*	38.0 (11.2)
CI ($L/min/m^2$)	*30*	5.8 (1.3)	*20*	7.3 (1.8)	*32*	6.4 (2.7)	*23*	6.6 (2.1)	*32*	6.4 (1.9)	*23*	6.2 (1.6)
LV function during recovery												
S’ (cm/s)	*32*	6.8 (1.3)	*23*	9.3 (2.1)	*31*	7.5 (1.5)	*26*	9.3 (1.9)	*32*	7.2 (1.3)	*25*	8.0 (1.0)
e’ (cm/s)	*32*	7.5 (1.4)	*23*	9.6 (1.8)	*31*	7.4 (1.6)	*26*	8.8 (1.7)	*32*	7.9 (1.8)	*25*	8.3 (1.8)

A' (cm/s)	*32*	4.3 (1.3)	*23*	4.7 (1.8)	*31*	4.8 (1.8)	*26*	5.3 (2.3)	*32*	5.0 (2.0)	*25*	4.9 (1.8)
Vascular function and cardiorespiratory fitness												
Baseline BA diameter (cm)	*19*	3.1 (0.5)	*14*	3.2 (0.3)	*11*	3.4 (0.4)	*14*	3.3 (0.4)	*17*	3.2 (0.3)	*11*	3.2 (0.4)
FMD (%)	*19*	6.2 (4.3)	*14*	4.1 (2.9)	*11*	7.4 (3.8)	*14*	5.1 (4.6)	*17*	6.7 (4.4)	*11*	7.6 (3.9)
$\dot{V}O_{2peak}$ (mL/kg/min)	*33*	31.2 (5.9)	*22*	36.6 (7.4)	*29*	32.2 (5.2)	*25*	33.6 (6.3)	*31*	31.6 (5.5)	*26*	32.2 (5.9)
$\dot{V}O_{2peak}$ ($mL/kg^{FFM}/min$)	*25*	58.8 (8.9)	*17*	64.5 (8.3)	*25*	59.9 (9.2)	*22*	59.7 (12.0)	*26*	59.8 (8.0)	*16*	57.6 (8.8)

HIIT, high intensity interval training; MICT, moderate intensity continuous training; S', peak systolic tissue velocity; e', peak early diastolic tissue velocity; A', peak late diastolic tissue velocity; GLS, global longitudinal strain; SR, strain rate; LVEDVi, left ventricular end diastolic volume index; LVESVi, left ventricular end systolic volume index; EF, ejection fraction; SVi, stroke volume index; CI, cardiac index; $\dot{V}max_{LVOT}$, maximal velocity in left ventricular outflow tract; FMD, flow mediated dilation; BA, brachial artery; $\dot{V}O_{2peak,}$ peak oxygen consumption; FFM, fat free mass

Table 3. Between group estimated mean differences for cardiac function, vascular function and cardiorespiratory fitness during rest, peak exercise and recovery

	HIIT versus MICT				HIIT versus NUTRITION				MICT versus NUTRITION				Int	Age	Sex
		95% CI				95% CI				95% CI					
Variable	**EMD**	**Low**	**Up**	**P**	**EMD**	**Low**	**Up**	**P**	**EMD**	**Low**	**Up**	**P**	**P**	**P**	**P**
LV function at rest															
S' (cm/s)	0.3	-0.2	0.9	0.24	1.0	0.5	1.6	<0.001	0.7	0.2	1.3	0.010	**0.001**	0.004	0.28
e' (cm/s)	0.7	-0.4	1.8	0.20	1.5	0.4	2.7	0.007	0.8	-0.3	1.9	0.15	**0.026**	0.51	0.19
A' (cm/s)	0.3	-0.2	0.9	0.26	0.3	-0.3	0.9	0.29	0.0	-0.6	0.5	0.96	0.45	0.022	0.57
GLS (%)	-1.0	-2.1	0.0	0.053	-1.7	-2.8	-0.6	0.002	-0.7	-1.8	0.4	0.21	**0.009**	0.016	0.053
SR (s^{-1})	-0.0	-0.1	0.0	0.36	-0.1	-0.2	-0.0	0.004	-0.1	-0.1	0.0	0.040	**0.018**	0.016	0.15
LVEDVi (mL/m^2)	4.8	-2.1	11.6	0.18	5.5	-1.4	12.3	0.12	0.7	-5.9	7.3	0.84	0.24	0.42	0.87
LVESVi (mL/m^2)	0.7	-3.8	5.2	0.77	1.0	-3.5	5.5	0.66	0.3	-4.0	4.6	0.89	0.91	0.68	0.25
EF (%)	4.0	0.1	8.0	0.045	6.2	2.3	10.1	0.002	2.2	-1.7	6.0	0.28	**0.007**	0.53	0.22
SVi (mL/m^2)	6.8	2.7	10.9	0.001	6.9	2.7	11.1	0.001	0.1	-3.9	4.0	0.96	**0.001**	0.44	0.66
CI ($L/min/m^2$)	0.0	-0.3	0.4	0.91	0.1	-0.3	0.4	0.74	0.0	-0.3	0.4	0.81	0.94	0.032	0.77

RV function at rest															
S’ (cm/s)	0.7	-0.4	1.8	0.20	1.2	0.1	2.3	0.032	0.5	-0.6	1.6	0.40	0.093	0.36	0.17
e’ (cm/s)	2.1	0.5	3.6	0.009	2.2	0.7	3.8	0.005	0.2	-1.4	1.7	0.83	**0.008**	0.39	0.083
A’ (cm/s)	1.1	-0.3	2.4	0.12	1.1	-0.3	2.4	0.12	0.0	-1.4	1.4	0.99	0.20	0.59	0.10
GLS (%)	-3.0	-5.5	-0.5	0.020	-4.3	-6.9	-1.7	0.001	-1.3	-3.8	1.2	0.32	**0.005**	0.098	0.43
SR (s^{-1})	-0.1	-0.3	0.1	0.46	-0.4	-0.6	-0.2	0.001	-0.3	-0.5	-0.1	0.005	**0.002**	0.79	0.27
LV function during peak exercise															
S' (cm/s)	0.1	-0.7	1.0	0.77	1.0	0.2	1.8	0.020	0.9	0.0	1.7	0.039	**0.040**	<0.001	0.19
e' (cm/s)	0.0	-0.9	0.9	0.95	0.3	-0.6	1.3	0.47	0.4	-0.6	1.3	0.43	0.68	0.004	0.15
$\dot{V}max_{LVOT}$ (m/s)	0.1	0.0	0.3	0.14	0.3	0.1	0.5	<0.001	0.2	0.0	0.3	0.029	**0.002**	0.020	0.12
SVi (mL/m^2) *	0.1	-0.1	0.3	0.21	0.3	0.1	0.4	0.003	0.1	0.0	0.3	0.066	**0.023**	0.77	0.67
CI ($L/min/m^2$) *	0.0	-0.1	0.1	0.82	0.0	-0.1	0.2	0.52	0.0	-0.1	0.2	0.67	0.81	0.071	0.66
LV function during recovery															
S’ (cm/s)	0.1	-0.7	0.9	0.76	1.4	0.6	2.2	0.001	1.2	0.5	2.0	0.002	**0.001**	<0.001	0.93

e' (cm/s)	0.6	-0.3	1.5	0.17	1.2	0.3	2.1	0.010	0.6	-0.3	1.4	0.21	**0.036**	0.89	0.71
A' (cm/s) *	-0.1	-0.3	0.1	0.4	0.0	-0.2	0.2	0.97	0.1	-0.1	0.3	0.32	0.57	0.26	0.80
Vascular function and cardiorespiratory fitness															
Baseline BA diameter (cm)	-0.1	-0.3	0.2	0.67	0.0	-0.2	0.2	0.92	0.0	-0.2	0.3	0.77	0.90	<0.001	0.079
FMD (%)	-0.9	-3.7	1.9	0.53	-4.2	-7.2	-1.2	0.005	-3.3	-6.3	-0.3	0.033	**0.025**	0.88	0.59
$\dot{V}O_{2peak}$ (mL/kg/min)	2.3	-0.1	4.6	0.062	4.1	1.7	6.4	0.001	1.8	-0.5	4.1	0.12	**0.003**	0.66	0.019
$\dot{V}O_{2peak}$ ($mL/kg^{FFM}/min$)	4.9	0.2	9.6	0.042	8.1	3.0	13.2	0.002	3.2	-1.6	8.0	0.19	**0.007**	0.85	0.012

Data are based on intention to treat analyses. HIIT, high intensity interval training; MICT, moderate intensity continuous training; Int, intervention effect; EMD, estimated mean difference; S', peak systolic tissue velocity; e', peak early diastolic tissue velocity; A', peak late diastolic tissue velocity; GLS, global longitudinal strain; SR, strain rate; LVEDVi, left ventricular end diastolic volume index; LVESVi, left ventricular end systolic volume index; EF, ejection fraction; SVi, stroke volume index; CI, cardiac index; $\dot{V}max_{LVOT}$; maximal velocity in left ventricular outflow tract; BA, brachial artery; FMD, flow mediated dilation; $\dot{V}O_{2peak,}$ peak oxygen consumption; FFM, fat free mass

* Model estimates presented in natural logarithmic (ln) scale.