Sports Med
DOI 10.1007/s40279-017-0777-0

ORIGINAL RESEARCH ARTICLE

Effect of High-Intensity Interval Training on Fitness, Fat Mass and Cardiometabolic Biomarkers in Children with Obesity: A Randomised Controlled Trial

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Abstract

Background Paediatric obesity significantly increases the risk of developing cardiometabolic diseases across the lifespan. Increasing cardiorespiratory fitness (CRF) could mitigate this risk. High-intensity interval training (HIIT) improves CRF in clinical adult populations but the evidence in paediatric obesity is inconsistent.

Objectives The objectives of this study were to determine the efficacy of a 12-week, HIIT intervention for increasing CRF and reducing adiposity in children with obesity.

Methods Children with obesity ($n = 99$, 7–16 years old) were randomised into a 12-week intervention as follows: (1) HIIT [$n = 33$, 4 × 4-min bouts at 85–95% maximum heart rate (HR_{max}), interspersed with 3 min of active recovery at 50–70% HR_{max}, 3 times/week] and nutrition advice; (2) moderate-intensity continuous training (MICT) [$n = 32$, 44 min at 60–70% HR_{max}, 3 times/week] and nutrition advice; and (3) nutrition advice only (nutrition) [$n = 34$]. CRF was quantified through a maximal exercise test ($\dot{V}O_{2peak}$) while adiposity was assessed using magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA) and air-displacement plethysmography.

Results HIIT stimulated significant increases in relative $\dot{V}O_{2peak}$ compared with MICT (+3.6 mL/kg/min, 95% CI 1.1–6.0, $P = 0.004$) and the nutrition intervention

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Electronic supplementary material The online version of this article (doi:10.1007/s40279-017-0777-0) contains supplementary material, which is available to authorized users.

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Published online: 29 August 2017

(+5.4 mL/kg/min, 95% CI 2.9–7.9, $P = 0.001$). However, the intervention had no significant effect on visceral and subcutaneous adipose tissue, whole body composition or cardiometabolic biomarkers ($P > 0.05$).

Conclusion A 12-week, HIIT intervention was highly effective in increasing cardiorespiratory fitness when compared with MICT and nutrition interventions. While there were no concomitant reductions in adiposity or blood biomarkers, the cardiometabolic health benefit conferred through increased CRF should be noted.

Clinical trials registration number Clinicaltrials.gov; NCT01991106.

Key Points

Twelve weeks of high-intensity interval training resulted in improvements in aerobic fitness among children with obesity.

The increase in fitness observed with this type of training was superior to increases observed following traditional, moderate intensity continuous training.

High-intensity interval training was unable to reduce the amount of abdominal and total body fat mass and had no effect on blood biomarkers.

1 Introduction

Paediatric obesity has reached levels of prevalence and severity that were inconceivable 50 years ago [1]. Children with obesity are at a significantly increased risk of developing cardiometabolic diseases such as diabetes mellitus, hypertension, coronary artery disease and stroke in childhood and adulthood [2]. Visceral adipose tissue (VAT), which can predict the development of obesity-related cardiometabolic disease [3] and is an independent predictor of all-cause mortality in men [4], is also increased in children with obesity compared with their healthy-weight counterparts [5]. Increased cardiorespiratory fitness (CRF) may negate the detrimental effect of obesity [6], conferring protection against the development of cardiometabolic diseases and associated risk factors in adults [7–9] and children [10, 11]. The inclusion of supervised exercise training in multi-disciplinary behavioural lifestyle interventions provides a potent stimulus for increasing CRF [12] and reducing adiposity [13–15]. Given that only 5–50% of children and adolescents meet current physical activity guidelines [16] and that children with obesity are less physically active compared with healthy-weight children [17], an efficacious exercise modality is desirable.

High-intensity interval training (HIIT), in the recommended 4 × 4 format, is twice as effective as moderate-intensity continuous training (MICT) for eliciting increases in CRF in adults [18]. A variety of HIIT protocols have been shown to improve cardiometabolic health outcomes in children with obesity [19–23]. Importantly, children express increased enjoyment during HIIT [24]. This could be attributed to the intermittent nature of HIIT, which is akin to spontaneous childhood play [25]. Increased enjoyment should promote high exercise adherence [26, 27] and in turn provide an effective exercise prescription. However, the efficacy of HIIT for improving objectively measured CRF in children with obesity remains unknown. While evidence in adults suggests that higher intensity exercise may be important for reducing VAT [28, 29], this is yet to be comprehensively studied in children with obesity.

Therefore, the aim of this investigation was to examine the effect of 12 weeks of HIIT and nutrition advice, MICT and nutrition advice, or nutrition advice only, on CRF and VAT in children with obesity. We hypothesised that HIIT would be more effective than MICT and nutrition advice only for increasing CRF, reducing VAT and improving blood biomarkers of cardiometabolic risk.

2 Subjects and Methods

Ninety-nine children with obesity [body mass index (BMI) percentile curves that pass through 30 kg/m^2 at age 18 years] [30] were recruited into a multicentre 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 2016. Over this time, 100 healthy-weight children (BMI percentile curves that pass through 18–25 kg/m^2 at age 18 years) [30] were assessed for comparative purposes and did not partake in the intervention. Participants' legal guardians provided consent, and participants provided written assent prior to participation. Detailed ethical approval, eligibility criteria, recruitment processes and randomisation procedures are outlined in the study protocol [31]. Briefly, exclusion criteria included hypertension, history or evidence of cardiac abnormalities, diabetes, smoking habits or orthopaedic/neurological disorders that limited exercise ability. An online randomisation system concealed group allocation and a permuted block design was used to randomise and stratify participants by age and sex following baseline assessments. Sample size was calculated for the primary outcome of the multicentre

randomised controlled trial (left ventricular function – peak systolic tissue velocity) [31].

Participant assessments were conducted in the university research laboratories at NTNU and UQ, and in hospital outpatient settings (St. Olav's Hospital, Trondheim and the Wesley Hospital, Brisbane). Detailed descriptions of physiological assessments have been published [31]. In brief, research staff or paediatricians completed a physical examination of basic anthropometric outcomes. Pubertal status was reported according to the Tanner stages of puberty [32, 33] either by a paediatrician (NTNU) or by participants (UQ). Additionally, the following outcomes were assessed: (1) cardiorespiratory fitness; (2) abdominal adipose tissue; (3) whole body composition; (4) lipids, triglycerides, glycaemic control and insulin resistance, ferritin, haemoglobin, and (5) leisure-time physical activity and nutrition. While equipment varied between centres, identical equipment was used for each individual at each assessment.

2.1 Cardiorespiratory Fitness

Participants performed 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). Calibration procedures have been outlined elsewhere [31]. After 3 min of rest, participants completed a 4-min warm-up at 4 km/h while they were familiarised with treadmill walking. During the maximal exercise test, treadmill inclination was increased by 2% each minute to a maximum gradient of 12–16%. Following this, treadmill speed was increased by 1 km/h each minute until volitional exhaustion. Heart rate was measured continuously during the test (Polar; Polar Electro, Kempele, Finland). Peak oxygen consumption ($\dot{V}O_{2_{peak}}$) was calculated as the average of the two highest 30-s values attained. One-minute heart rate recovery (HRR-1) was calculated as [maximum heart rate – heart rate at 1 min post-exercise test cessation].

2.2 Abdominal Adipose Tissue and Total Body Composition

MRI scans of abdominal adipose tissue were obtained using a 1.5 T unit in Brisbane (Siemens Symphony Sonata) and a 3 T unit in Trondheim, as previously detailed [31]. In summary, axial slices centred over the L4–L5 intervertebral disc were acquired during breath hold (14 × 8 mm slices in Brisbane; 52 × 3 mm in Trondheim). MRI scans were anonymised and analysed by a single investigator blinded to group allocation using SliceOmatic (Version 5.0; Tomovision, Magog, Canada). To account for the differences in scanning protocols between the two sites, raw data collected in Trondheim was modified whereby 3 × 3 mm slices were combined to form a 9 mm slice. Twelve slices were analysed, covering 112 mm of torso centred over the L4–L5 intervertebral disc. This allowed data from UQ and NTNU to be combined for statistical analyses. Scan metadata (slice thickness) was used by the software to automatically calculate volumes. Average subcutaneous adipose tissue (SAT) and VAT cross-sectional area (CSA), and total SAT and VAT volume were calculated. Total abdominal adipose tissue (TAAT) volume was calculated as the sum of SAT and VAT volume. If the SAT area was incomplete owing to the scanning field of view on both sides of the image, only VAT outcomes were reported. If the SAT area was incomplete on one side of the image only, SAT was calculated for the available half and was doubled to provide complete SAT and TAAT measurements ($n = 16$). Intra-observer SAT and VAT analysis coefficient of variation was 0.7 and 3.6%, respectively. Total body fat percentage, total fat mass and total fat-free mass (FFM) were assessed using dual-energy X-ray absorptiometry (DXA) in Brisbane (Discovery^{TM} DXA System; Hologic QDR Series, Bedford, MA, USA) and air-displacement plethysmography in Trondheim (BodPod; COSMED, Rome, Italy).

2.3 Biochemical Analyses

Detailed serum and plasma collection procedures have been outlined elsewhere [31]. Samples were analysed for fasting lipids and triglycerides, fasting glucose, glycosylated haemoglobin (HbA_{1c}) [Rx Daytona Plus; Randox Laboratories, Crumlin, County Antrim, UK; Modular P; Roche Diagnostics, Indianapolis, IN, USA; Cobas Integra 400; Roche Diagnostics, Indianapolis, IN, USA], C peptide (electrochemiluminescence immunoassay [ECLIA], Cobas e411 immunoassay analyser; Roche Diagnostics; IMMULITE 2000; Siemens HealthCare GmbH, Erlangen, Germany), ferritin (electrochemiluminescence immunoassay [ECLIA], Cobas e411 immunoassay analyser, Cobas 8000 e602; Roche Diagnostics) and haemoglobin [standard cyanmethemoglobin (Drabkin's) method; Sysmex XN; Sysmex Corporation, Kobe, Japan]. The Homeostatic Model Assessment was used to calculate insulin resistance (HOMA-IR) via the HOMA2 calculator Version 2.2.3 [34]. The coefficients of variation for the outcomes were as follows: at UQ: cholesterol (1.0%), high-density lipoprotein (1.0%), triglycerides (1.4%), fasting glucose (0.6%), C peptide (0.8%), HbA_{1c} (2.7%), ferritin (1.6%) and haemoglobin (1.4%); at NTNU: cholesterol (2.5%), high-density lipoprotein (2.8%), triglycerides (3.4%), fasting

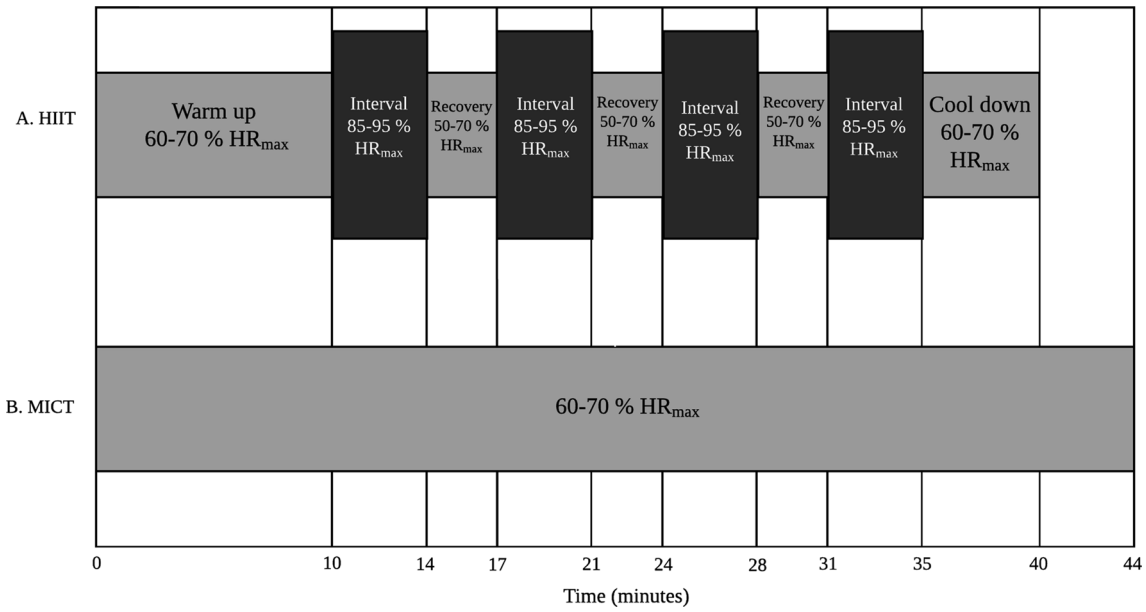

Fig. 1 Schematic detailing time and intensity of **a** high-intensity interval training (HIIT) and **b** moderate-intensity continuous training (MICT). HR_{max} maximum heart rate

glucose (2.1%), C peptide (4.1%), HbA_{1c} (1.5%), ferritin (4.3%) and haemoglobin (0.8%).

2.4 Leisure-Time Physical Activity and Nutrition

Participants were asked to wear an accelerometer for 7 days prior to and following the 12-week intervention (UQ: ActiGraph LCC, Pensacola, FL, USA and NTNU: SenseWear; BodyMedia, Inc., Pittsburgh, PA, USA). Details of analysis software, initialisation procedures, wear time criteria and cut points have been previously published [31].

Participants completed 3- to 4-day (inclusive of 1 weekend day) food records. Data were analysed using FoodWorks (Xyris Software, Brisbane, QLD, Australia) for the Australian cohort and using the food database KBS AE-07 and KBS software system (KBS, Version 4.9, 2008; Department of Nutrition, University of Oslo, Oslo, Norway) for participants in Norway.

2.5 Interventions

Participants with obesity were randomised to one of three groups: (1) HIIT; (2) MICT; or (3) nutrition advice only. The exercise groups (HIIT and MICT) trained three times each week for 12 weeks and all participants received between four and six, 20–30 min nutrition consultations with a dietitian over the 12-week period. Exercise protocols are outlined in Fig. 1 and are further detailed in the study protocol [31]. Individual nutrition sessions were location specific and were based on current Norwegian [35] and Australian [36] dietary guidelines with a particular focus on healthy food choices, portion sizes and regular meal times.

2.6 Statistical Analysis

Descriptive data are presented as mean ± standard deviation if continuous, and counts (percentages) if categorical. A linear regression was used to estimate differences between obese and healthy-weight children at baseline, accounting for age, sex and centre. Differences between the interventions and within-group effects of the intervention were analysed using linear mixed models (LMMs), adjusting for age, sex and centre, and allowing for a heterogeneous residual variance between centres. 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). Within- and between-group pairwise differences were calculated using post-hoc 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 or Anderson–Darling tests. Where outcomes of interest were transformed to satisfy model assumptions, the model parameter estimates are presented in the natural logarithmic (ln) transformed scale.

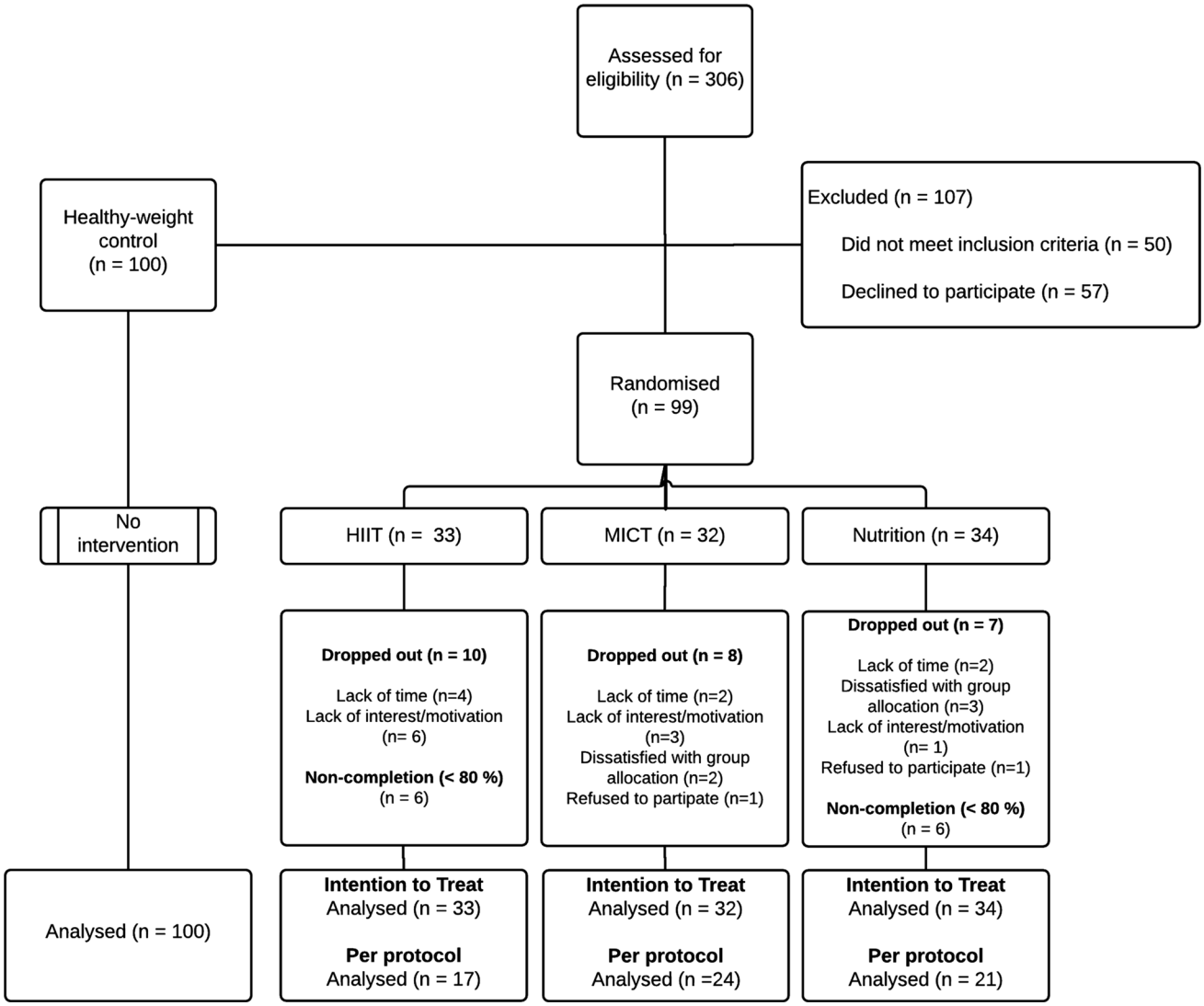

Fig. 2 CONSORT flow chart for the multicentre randomised controlled trial. *HIIT* high-intensity interval training, *MICT* moderate-intensity continuous training

Intention-to-treat (HIIT = 33; MICT = 32; nutrition = 34) and per-protocol analyses (HIIT = 17; MICT = 24; nutrition = 21) were conducted using LMMs. All available data were included in the intention-to-treat analysis and it was assumed that data were missing at random, which is allowed for in the LMM. 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) × 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, but results were interpreted taking multiple testing into consideration.

3 Results

A CONSORT diagram (Fig. 2) summarises participant flow through each stage of the trial and outlines reasons for participant drop out. All available data for participants were included in the intention-to-treat analysis and have been presented in a tabular format. Fifty children with obesity and 42 children with healthy weight consented and were willing to undergo the MRI scan. Two MRI scans acquired in children with obesity could not be analysed owing to considerable motion artefact and incorrect slice positioning.

Sixty-two out of ninety-nine (63%) participants successfully completed the trial and were included in the per-protocol analysis. Post-hoc pairwise comparisons for the

Table 1 Baseline data and comparisons between healthy-weight and obese children. Estimated mean differences (EMD), 95% confidence intervals (95% CI) and *P* values were calculated using a linear regression accounting for age, sex and centre

Variable	Obese		Healthy weight		Obese vs. healthy weight			
	n	Mean ± SD	*n*	Mean ± SD	EMD	95% CI		*P* value
						Lower	Upper	
$\dot{V}O_{2_{peak}}$ (L/min)	93	2.31 ± 0.64	97	2.22 ± 0.87	−0.01	−0.15	0.13	0.858
$\dot{V}O_{2_{peak}}$ (mL/kg/min)	93	31.6 ± 5.5	97	52.9 ± 8.4	−21.2	−23.1	−19.3	<0.001
$\dot{V}O_{2_{peak}}$ (mL/kg^{FFM}/min)	76	59.5 ± 8.6	96	68.1 ± 9.4	−9.6	−11.8	−7.4	<0.001
VAT volume (cm^3)	48	748 ± 235	42	193 ± 89	551	477	624	<0.001
SAT volume (cm^3)	43	4389 ± 1282	41	927 ± 465	3464	3085	3842	<0.001
TAAT volume (cm^3)	43	5065 ± 1497	41	1118 ± 514	3952	3512	4392	<0.001
Weight (kg)	99	74.4 ± 19.1	100	41.2 ± 12.2	30.1	27.4	32.8	<0.001
Body mass index (kg/m^2)	99	29.5 ± 4.4	100	17.6 ± 2.1	11.5	10.7	12.3	<0.001
Body mass index *z*-score	99	2.14 ± 0.29	100	−0.13 ± 0.63	2.27	2.13	2.41	<0.001
Total body fat (%)	80	44.1 ± 6.2	99	19.5 ± 7.5	24.0	22.3	25.8	<0.001
Total fat mass (kg)	80	31.3 ± 10.6	99	7.7 ± 3.6	1.40[a]	1.30	1.50	<0.001
Total FFM (kg)	80	38.9 ± 10.2	99	32.3 ± 10.7	5.9	4.1	7.6	<0.001
HRR-1 (bpm)	83	40 ± 12	95	44 ± 16	0.00[a]	−0.09	0.09	0.974
Cholesterol (mmol/L)	82	4.11 ± 0.84	90	4.20 ± 0.69	−0.05	−0.28	0.18	0.660
HDL (mmol/L)	82	1.26 ± 0.26	90	1.73 ± 0.32	−0.46	−0.55	−0.38	<0.001
LDL (mmol/L)	82	2.37 ± 0.72	90	2.19 ± 0.56	0.21	0.01	0.40	0.037
Triglycerides (mmol/L)	82	1.06 ± 0.55	90	0.61 ± 0.26	0.51[a]	0.38	0.64	<0.001
Fasting glucose (mmol/L)	82	5.08 ± 0.40	90	4.86 ± 0.32	0.21	0.10	0.32	<0.001
HbA_{1c} (%)	76	5.31 ± 0.29	86	5.13 ± 0.23	0.04[a]	0.02	0.05	<0.001
C peptide (nmol/L)	84	0.93 ± 0.45	90	0.41 ± 0.21	0.78[a]	0.65	0.90	<0.001
HOMA-IR	82	2.06 ± 1.02	89	0.88 ± 0.46	0.80	0.67	0.93	<0.001
Ferritin (ng/mL)	82	52.6 ± 26.6	90	39.3 ± 19.5	0.32[a]	0.17	0.47	<0.001
Haemoglobin (g/dL)	77	13.6 ± 0.9	87	13.6 ± 0.8	−0.08	−0.32	0.17	0.529
Energy intake (kJ/day)	56	7996 ± 2808	97	7232 ± 2691	0.08[a]	−0.04	0.20	0.198
Light activity (min/day)	56	200 ± 142	23	253 ± 83	−0.24[a]	−0.48	0.01	0.058
Moderate activity (min/day)	56	45 ± 116	23	28 ± 23	−0.27[a]	−0.55	0.12	0.063
Vigorous activity (min/day)	56	6 ± 7	23	11 ± 11	−9	−17	−1	0.028

FFM fat-free mass, *HbA$_{1c}$* glycosylated haemoglobin, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model of insulin resistance, *HRR-1* heart rate recovery at 1 min, *LDL* low-density lipoprotein, *SAT* subcutaneous adipose tissue, *SD* standard deviation, *TAAT* total abdominal adipose tissue, *VAT* visceral adipose tissue, *$\dot{V}O_{2_{peak}}$* peak oxygen consumption

[a] Model estimates presented in natural logarithmic (ln) scale

per-protocol and intention-to-treat analyses differed for only one outcome ($\dot{V}O_{2_{peak}}$ relative to body weight) and results from the per-protocol analysis are presented in the text and Fig. 3. All remaining results are calculated from the intention-to-treat analysis.

3.1 Clinical Characteristics

A summary of baseline characteristics and a comparison of outcomes of interest for obese and healthy-weight children are presented in Table 1. There were no differences in age, sex or Tanner stage of puberty between the populations [obese: age 12.0 ± 2.3 years, 53 (53.5%) female, Tanner stage 2 (2–4); healthy weight: age 11.5 ± 2.4 years, 50 (51.0%) female, Tanner stage 2 (1–3)]. Children with obesity had significantly greater body mass, BMI *z*-score, total body fat percent, VAT, and SAT compared with healthy-weight children ($P < 0.001$ for all comparisons). They also had significantly lower CRF ($P < 0.001$) and engaged in less leisure time vigorous activity each day ($P = 0.028$). Furthermore, children with obesity had elevated traditional cardiovascular risk factors including

Table 2 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

Data shown for participants who completed the intervention (per-protocol analysis)

HIIT high-intensity interval training, *HR* heart rate, HR_{max} maximum heart rate, *MICT* moderate-intensity interval training

significantly lower high-density lipoprotein ($P < 0.001$) and ferritin ($P < 0.001$), and significantly higher low-density lipoprotein ($P = 0.037$), triglycerides ($P < 0.001$), fasting glucose ($P < 0.001$), HbA_{1c} ($P < 0.001$), C peptide ($P < 0.001$) and HOMA-IR ($P < 0.001$) when compared with their healthy-weight counterparts.

3.2 Intervention Effects in Children with Obesity

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

A summary of adipose tissue, cardiorespiratory fitness, blood biochemistry, physical activity and nutrition outcomes at baseline and post-intervention is presented for each group in Table 3. Table 4 presents the estimated between-group intervention effects including the estimated mean difference (EMD), 95% confidence interval (CI) and *P* values for all outcomes. Linear mixed models were fitted to include an interaction effect between centre and intervention. However, this interaction effect was only significant for six outcome variables ($P > 0.02$ for all but one variable). In light of multiple testing, and for ease of interpretation and generalisability of findings, the results presented are for models without this interaction effect, but were adjusted for centre by a main effect. Model parameters were also adjusted for age and sex. The *P* values for the effects of age and sex on each outcome are also provided in Table 4. Within-group intervention effects (EMD, 95% CI and *P* values) are presented in the Electronic Supplementary Material.

3.2.1 Cardiorespiratory Fitness

The exercise interventions significantly increased CRF as indicated by both intention-to-treat (Table 4) and per-protocol analyses (Fig. 3a, c). Twelve weeks of HIIT resulted in significantly greater improvements in relative $\dot{V}O_{2_{peak}}$ than 12 weeks of MICT as revealed by the per-protocol analysis (EMD 3.6 mL/kg/min, 95% CI 1.1–6.0, $P = 0.004$). Furthermore, HIIT was more effective than the nutrition-only intervention in increasing CRF (per protocol: EMD 5.4 mL/kg/min, 95% CI 2.9–7.9, $P < 0.001$). Conversely, MICT did not confer greater increases in CRF than the nutrition-only intervention (per protocol: EMD 1.8 mL/kg/min, 95% CI −0.5 to 4.1, $P = 0.120$).

3.2.2 Abdominal Adipose Tissue and Whole Body Composition

There were no significant changes in VAT, SAT or TAAT between the interventions (Fig. 3b, d). Participant height increased equally between groups over the intervention ($P = 0.839$) and it is unlikely that growth affected abdominal adipose tissue measurements. There was no significant intervention effect on fat percentage, fat mass, FFM, weight, BMI or BMI *z*-score.

3.2.3 Blood Biochemistry, Physical Activity and Nutrition

The 12-week MICT intervention significantly improved HbA_{1c} compared with the nutrition-only intervention (EMD −0.15 percentage points, 95% CI −0.27 to −0.04, $P = 0.009$). The MICT intervention saw significant within-group reductions in HbA_{1c} (EMD −0.11 percentage points, 95% CI −0.19 to −0.03, $P = 0.005$) while no within-

Table 3 Baseline and post-intervention data for the intervention groups

Variable	HIIT				MICT				Nutrition			
	Baseline		Post		Baseline		Post		Baseline		Post	
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
$\dot{V}O_{2_{peak}}$ (L/min)	33	2.24 ± 0.58	22	2.55 ± 0.59	29	2.43 ± 0.68	25	2.28 ± 0.60	31	2.28 ± 0.66	26	2.30 ± 0.65
$\dot{V}O_{2_{peak}}$ (mL/kg/min)	33	31.2 ± 5.9	22	36.6 ± 7.4	29	32.2 ± 5.23	25	33.6 ± 6.3	31	31.6 ± 5.5	26	32.2 ± 5.9
$\dot{V}O_{2_{peak}}$ (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
VAT volume (cm^3)	15	630 ± 127	15	660 ± 168	18	791 ± 211	17	793 ± 189	15	816 ± 305	14	803 ± 252
SAT volume (cm^3)	13	4381 ± 1023	14	4274 ± 919	17	4229 ± 1510	16	4121 ± 1205	13	4607 ± 1259	11	4541 ± 1269
TAAT volume (cm^3)	13	5004 ± 1072	14	4910 ± 1019	17	4857 ± 1893	16	4982 ± 1274	13	5399 ± 1317	11	5343 ± 1421
Weight (kg)	33	72.3 ± 16.8	23	70.7 ± 12.9	32	76.6 ± 21.6	25	72.8 ± 20.6	34	74.3 ± 19.1	26	72.8 ± 20.5
Body mass index (kg/m^2)	33	28.8 ± 3.8	23	28.1 ± 3.6	32	30.4 ± 5.0	25	29.1 ± 4.8	34	29.6 ± 4.3	26	28.7 ± 4.7
Body mass index z-score	33	2.01 ± 0.25	23	1.93 ± 0.34	32	2.22 ± 0.31	25	2.12 ± 0.37	34	2.17 ± 0.28	26	2.08 ± 0.31
Total body fat (%)	25	44.7 ± 7.3	18	43.4 ± 7.1	27	43.8 ± 5.4	22	42.6 ± 6.0	28	43.8 ± 6.1	16	42.9 ± 6.5
Total fat mass (kg)	25	31.9 ± 10.9	18	31.0 ± 8.6	27	30.9 ± 10.5	22	30.2 ± 10.7	28	31.1 ± 10.9	16	29.8 ± 10.3
Total FFM (kg)	25	38.6 ± 9.1	18	40.2 ± 8.2	27	39.2 ± 11.1	22	40.1 ± 11.7	28	38.9 ± 10.6	16	38.2 ± 10.0
HRR-1 (bpm)	29	43 ± 10	20	45 ± 13	27	38 ± 12	25	46 ± 12	27	38 ± 14	22	43 ± 10
Cholesterol (mmol/L)	27	4.05 ± 0.82	19	3.79 ± 0.64	26	4.17 ± 0.86	22	4.26 ± 0.87	29	4.12 ± 0.89	19	4.25 ± 0.81
HDL (mmol/L)	27	1.23 ± 0.20	19	1.24 ± 0.27	26	1.30 ± 0.29	22	1.25 ± 0.26	29	1.24 ± 0.29	19	1.30 ± 0.31
LDL (mmol/L)	27	2.32 ± 0.69	19	2.10 ± 0.50	26	2.43 ± 0.77	22	2.55 ± 0.84	29	2.36 ± 0.73	19	2.36 ± 0.70
Triglycerides (mmol/L)	27	1.06 ± 0.44	19	0.96 ± 0.37	26	0.97 ± 0.51	22	1.00 ± 0.47	29	1.14 ± 0.66	19	1.26 ± 0.73
Fasting glucose (mmol/L)	27	5.07 ± 0.37	19	5.13 ± 0.37	26	5.10 ± 0.40	*22*	5.19 ± 0.37	29	5.08 ± 0.44	17	5.08 ± 0.39
HbA_{1c} (%)	25	5.33 ± 0.25	18	5.35 ± 0.30	23	5.30 ± 0.37	*22*	5.17 ± 0.22	28	5.31 ± 0.25	18	5.37 ± 0.23
C peptide (nmol/L)	28	0.92 ± 0.50	20	0.89 ± 0.49	27	0.93 ± 0.42	23	0.95 ± 0.34	29	0.94 ± 0.45	17	0.89 ± 0.33
HOMA-IR	27	2.07 ± 1.15	19	2.02 ± 1.10	26	2.05 ± 0.97	21	2.16 ± 0.80	29	2.06 ± 0.97	15	1.97 ± 0.79
Ferritin (ng/mL)	28	49.0 ± 20.3	17	42.4 ± 16.9	27	60.9 ± 26.4	24	59.7 ± 17.9	27	48.1 ± 31.3	24	44.3 ± 27.4
Haemoglobin (g/dL)	25	13.8 ± 0.9	17	13.6 ± 1.2	24	13.2 ± 1.0	22	13.5 ± 1.2	28	13.6 ± 0.9	18	13.6 ± 0.7
Energy intake (kJ/day)	20	7814 ± 3162	13	6825 ± 2747	18	7678 ± 2322	14	6756 ± 3611	18	8515 ± 2918	15	7192 ± 3008
Light activity (min/day)	18	171 ± 203	14	135 ± 174	21	210 ± 142	17	209 ± 207	17	226 ± 197	10	196 ± 85
Moderate activity (min/day)	18	53 ± 63	14	56 ± 59	21	50 ± 141	17	79 ± 123	17	30 ± 110	10	31 ± 28
Vigorous activity (min/day)	18	5 ± 12	14	7 ± 12	21	5 ± 7	17	8 ± 12	17	9 ± 6	10	7 ± 5

All available data are presented. Minor discrepancies between variables are the result of different subsamples for each outcome

FFM fat-free mass, *HbA_{1c}* glycosylated haemoglobin, *HDL* high-density lipoprotein, *HIIT* high-intensity interval training, *HOMA-IR* homeostatic model of insulin resistance, *HRR-1* heart rate recovery at 1 min, *LDL* low-density lipoprotein, *MICT* moderate-intensity continuous training, *SAT* subcutaneous adipose tissue, *SD* standard deviation, *TAAT* total abdominal adipose tissue, *VAT* visceral adipose tissue, *$\dot{V}O_{2_{peak}}$* peak oxygen consumption

Table 4 Between-group estimated mean differences (EMDs) for the intervention groups (intention-to-treat analysis)

Variable	HIIT vs. MICT				HIIT vs. nutrition				MICT vs. nutrition				Int	Age	Sex
	EMD	95% CI		*P* value	EMD	95% CI		*P* value	EMD	95% CI		*P* value	*P* value	*P* value	*P* value
		Low	Up			Low	Up			Low	Up				
$\dot{V}O_{2peak}$ (L/min)	0.17	−0.01	0.36	0.062	0.22	0.04	0.41	0.017	0.05	−0.13	0.23	0.616	0.049	<0.001	0.003
$\dot{V}O_{2peak}$ (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	0.122	0.003	0.660	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	0.188	0.007	0.846	0.012
VAT (cm^3)	4	−86	95	0.924	47	−48	141	0.333	42	−51	135	0.375	0.579	0.067	0.110
SAT (cm^3)	−91	−326	143	0.446	−140	−395	114	0.280	−49	−296	197	0.696	0.520	<0.001	0.148
TAAT (cm^3)	−34	−299	231	0.803	−92	−374	190	0.523	−58	−335	218	0.680	0.798	<0.001	0.137
Weight (kg)	−0.3	−2.2	1.7	0.800	−0.7	−2.7	1.2	0.473	−0.5	−2.4	1.5	0.638	0.789	<0.001	0.259
Body mass index (kg/m^2)	0.0	−0.8	0.7	0.946	0.0	−0.7	0.7	0.982	0.0	−0.7	0.7	0.963	0.998	<0.001	0.973
Body mass index *z*-score	0.00	−0.08	0.08	0.948	−0.01	−0.09	0.07	0.888	0.00	−0.08	0.08	0.941	0.994	0.681	0.106
Total body fat (%)	−0.5	−1.8	0.7	0.409	−0.9	−2.2	0.4	0.182	−0.4	−1.6	0.9	0.577	0.394	0.008	0.823
Total fat mass (kg)	0.1	−1.2	1.5	0.867	−0.5	−1.9	0.9	0.498	−0.6	−1.9	0.8	0.388	0.650	<0.001	0.447
Total FFM (kg)	0.5	−0.4	1.4	0.272	0.4	−0.5	1.4	0.377	−0.1	−1.0	0.9	0.892	0.498	<0.001	0.257
HRR-1 (bpm)	−3	−9	1	0.176	0	−6	5	0.869	3	−2	9	0.227	0.362	0.001	<0.001
Cholesterol (mmol/L)	−0.03	−0.33	0.26	0.825	−0.03	−0.33	0.28	0.855	0.00	−0.28	0.29	0.973	0.972	0.017	0.389
HDL (mmol/L)[a]	0.04	−0.03	0.11	0.249	0.02	−0.05	0.10	0.553	−0.02	−0.09	0.05	0.581	0.505	<0.001	0.890
LDL (mmol/L)	−0.04	−0.32	0.23	0.756	0.01	−0.27	0.30	0.929	0.06	−0.22	0.33	0.681	0.906	0.102	0.612
Triglycerides (mmol/L)[a]	−0.15	−0.35	0.06	0.162	−0.16	−0.37	0.05	0.134	−0.01	−0.22	0.19	0.896	0.260	0.324	0.620
Fasting glucose (mmol/L)[a]	0.00	−0.04	0.04	0.999	0.02	−0.03	0.06	0.464	0.02	−0.02	0.06	0.456	0.688	0.183	0.781
HbA_{1c} (%)	0.08	−0.03	0.20	0.161	−0.07	−0.19	0.05	0.272	−0.15	−0.27	−0.04	0.009	0.029	0.566	0.624
C peptide (nmol/L)[a]	−0.17	−0.35	0.02	0.074	−0.08	−0.28	0.12	0.417	0.09	−0.11	0.28	0.378	0.215	<0.001	0.137
HOMA-IR[a]	−0.02	−0.18	0.14	0.813	0.02	−0.16	0.19	0.830	0.04	−0.14	0.21	0.667	0.942	<0.001	0.158
Ferritin (ng/mL)	−9.35	−20.32	1.61	0.095	−4.23	−16.26	7.80	0.490	5.12	−5.67	15.91	0.353	0.231	0.712	<0.001
Haemoglobin (g/dL)	−0.10	−0.46	0.27	0.589	−0.28	−0.66	0.11	0.160	−0.18	−0.53	0.18	0.328	0.345	0.122	0.013
Energy intake (kJ/day)[a]	−0.02	−0.24	0.20	0.874	−0.12	−0.34	0.11	0.305	−0.10	−0.33	0.13	0.406	0.522	0.788	0.014
Light activity (min/day)[a]	−0.01	−0.15	0.14	0.940	−0.05	−0.20	0.10	0.502	−0.05	−0.18	0.09	0.511	0.684	<0.001	0.035
Moderate activity (min/day)[a]	0.00	−0.31	0.31	0.985	0.02	−0.32	0.35	0.923	0.01	−0.30	0.33	0.933	0.997	<0.001	0.874
Vigorous activity (min/day)[a]	−0.34	−0.82	0.14	0.161	−0.07	−0.55	0.41	0.773	0.27	−0.17	0.71	0.231	0.268	0.009	0.030

CI confidence interval, *FFM* fat-free mass, *HbA_{1c}* glycosylated haemoglobin, *HDL* high-density lipoprotein, *HIIT* high-intensity interval training, *HOMA-IR* homeostatic model of insulin resistance, *HRR-1* heart rate recovery at 1 min, *Int* intervention effect, *LDL* low-density lipoprotein, *MICT* moderate-intensity continuous training, *SAT* subcutaneous adipose tissue, *TAAT* total abdominal adipose tissue, *VAT* visceral adipose tissue, *$\dot{V}O_{2peak}$* peak oxygen consumption

[a] Model estimates presented in natural logarithmic (ln) scale

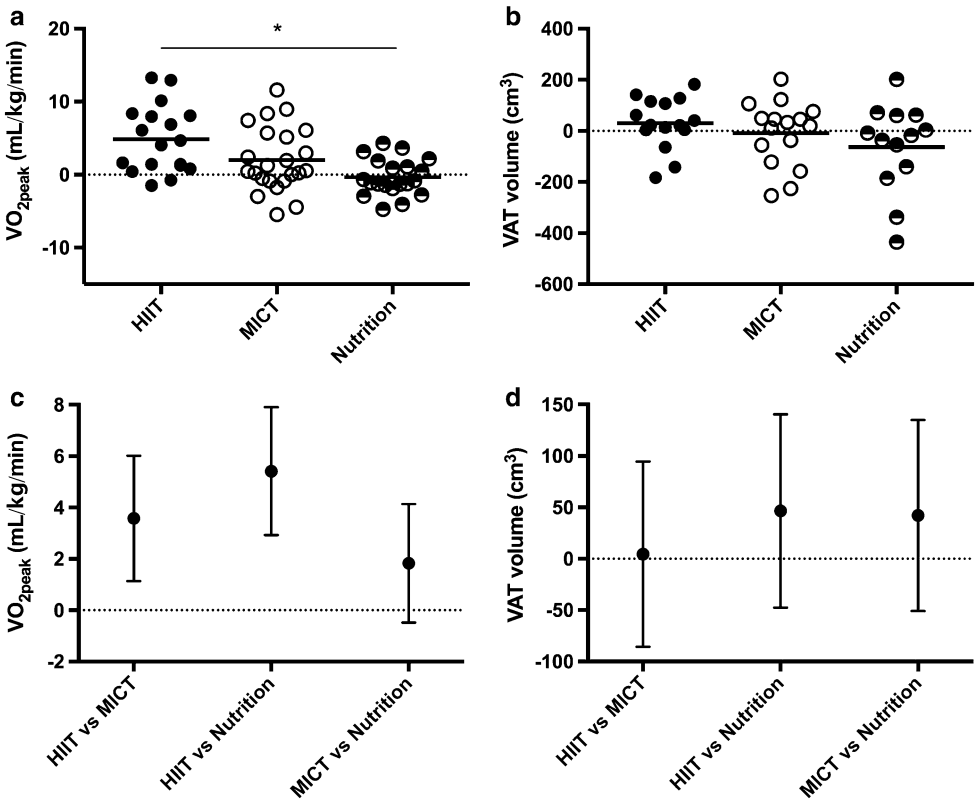

Fig. 3 Effect of the interventions on peak oxygen consumption [$\dot{V}O_{2peak}$] (**a**, **c**) and visceral adipose tissue [VAT] (**b**, **d**). **a** and **b** illustrate the mean (*horizontal bar*) and individual (*circles*) change scores for each intervention group while **c** and **d** show between-group comparisons (estimated mean difference and 95% confidence intervals). *Significant intervention effect ($P = 0.003$). Per-protocol data are shown for $\dot{V}O_{2peak}$ (**a**, **c**). *HIIT* high-intensity interval training, *MICT* moderate-intensity continuous training

group differences were observed for the HIIT and nutrition interventions. All other blood biochemical outcomes, as well as average daily time spent in light, moderate and vigorous physical activity, and average daily energy intake remained unchanged as an effect of the intervention.

4 Discussion

This multicentre randomised controlled trial is the largest HIIT study in paediatric obesity to date, and we have shown that HIIT was superior to MICT for eliciting improvements in CRF, but not for reducing fat mass or cardiometabolic biomarkers. With a similar training duration (HIIT 40 min vs. MICT 44 min), 12 weeks of HIIT induced increases in $\dot{V}O_{2peak}$ (13.5%, 4.2 mL/kg/min), which were more than twofold greater than increases following MICT (6.2%, 2.0 mL/kg/min). Furthermore, this is the first study to compare the efficacy of a HIIT, MICT and nutrition-only intervention on VAT and SAT volume in children with obesity. While it has been suggested that higher exercise intensities may be important for decreasing abdominal adipose tissue, particularly visceral depots, in adult populations [37], we found no evidence that a 12-week HIIT intervention was more effective for reducing adiposity than MICT or nutrition advice only in children with obesity. Therefore, while HIIT should be promoted among children with obesity as a potent stimulus for increasing CRF, it is not a successful short-term strategy for reducing abdominal or total adipose tissue.

Our demonstration that HIIT is significantly more effective than MICT for increasing $\dot{V}O_{2peak}$ in children with obesity is supported by a single previous investigation in this population [38]. While Starkoff et al. did not find a significant intervention effect on relative $\dot{V}O_{2peak}$, HIIT resulted in a significantly greater percentage change in $\dot{V}O_{2peak}$ compared with MICT (15.1 vs. 0.1%). To our knowledge, there are five further studies comparing the efficacy of HIIT vs. MICT for improving CRF in paediatric obesity. However, these either found no intervention effects on CRF [20, 21, 23] or did not perform between-group statistical analyses [22, 39]. In line with the magnitude of our findings, a meta-analysis in adults with cardiometabolic disease found a mean difference of 3.0 mL/kg/min between HIIT (19.4% increase) and MICT (10.3% increase) interventions [18]. In this analysis, seven out of ten included studies employed the 4 × 4 HIIT protocol used in this study [18]. As the three intervention groups completed similar levels of physical activity at baseline, it is plausible that the effect of MICT may have been masked, potentially owing to an insufficient exercise volume. However, it is important to note that the CRF of obese

participants was significantly lower than their healthy counterparts (VO_{2peak} normalised to body mass and FFM). Given this discrepancy, and the health implications of low CRF, it is important to find exercise modalities that are able to increase VO_{2peak} regardless of baseline physical activity levels. Importantly, the increases in $\dot{V}O_{2peak}$ observed after 12 weeks of HIIT in our cohort are likely to confer significant cardioprotective benefits. In adults, a 3.5-mL/kg/min increase in VO_{2peak}, equivalent to one metabolic equivalent (MET), is associated with a 10–25% improvement in survival [40]. Although the prognostic significance of this may be difficult to actualise in a paediatric population, our cohort of children with obesity illustrated significantly worse cardiometabolic health parameters in comparison to their healthy-weight counterparts. Given that up to 50% of obese children become obese adults [41], it is pertinent that risk factors are mitigated wherever possible. CRF is a modifiable risk factor that can outweigh the detrimental consequences of obesity [6], and we have shown that HIIT is a highly efficacious modality to achieve this in paediatric obesity.

This investigation has illustrated that a HIIT intervention combined with nutrition advice is no more effective for reducing abdominal adipose tissue or total body fat percent than a combination of MICT and nutrition advice, or nutrition advice only. To date, there is no evidence to suggest a dose–response relationship between exercise intensity and adipose tissue loss in paediatric obesity. Most recently, Hay et al. illustrated that 6 months of high-intensity endurance training (3 times per week for 30–40 min at 70–80% of heart rate reserve [HRR]) was unable to significantly decrease percentage body fat, or VAT CSA in children with obesity when compared with MICT (3 times per week for 30–40 min at 40–55% of HRR) and a non-exercising control group [42]. This finding is supported by a previous single study in this population that reported no difference between high- and moderate-intensity exercise for the reduction of VAT [43]. When total energy expenditure is held equal between exercise modalities, higher intensities should result in greater visceral adipose tissue lipolysis. High-intensity exercise such as HIIT results in a significantly greater release of catecholamines and growth hormone [28], which should stimulate adipose lipolysis resulting in increased free fatty acid (FFA) availability for use in working muscle tissue [29]. Although higher intensity exercise may result in increased FFA lipolysis, this does not directly translate to increased FFA oxidation, as a proportion of FFAs are likely to be re-esterified [44]. Furthermore, analogous to observations in adults with obesity [45, 46], children with obesity have attenuated growth hormone and catecholamine responses to acute exercise [47]. Eliakim et al. showed that the release of growth hormone, epinephrine, norepinephrine and dopamine following an acute bout of high-intensity cycling exercise in children with obesity was less than half of the response observed in healthy-weight children. If increased lipolysis and FFA levels via greater hormone release is the proposed pathway for HIIT to stimulate VAT reduction, then children with obesity are disadvantaged as a function of obesity per se. For HIIT to effectively target VAT reduction as per the postulated mechanisms, it could be speculated that weight loss must be achieved prior to attempting preferential VAT reduction with high-intensity exercise modalities. This approach may involve caloric restriction to lose body weight [48] prior to commencing a HIIT program, to target VAT loss more effectively. Notably, studies that elicited significant reductions in VAT in children with obesity used high-volume training protocols (60 min, 3–5 times/week) over 3 [49, 50] and 8 months [43], which emphasises the importance of exercise volume for the reduction of VAT, SAT and percentage body fat. For adults, at least 13 MET hours per week are recommended to significantly decrease total and abdominal adipose tissue [51], which equates to 30 min of brisk walking (6.4 km/h) over 5 days/week, or jogging (9.6 km/h) for 15 min over 3 days/week. Although we acknowledge that these guidelines are for adults, this level of evidence continues to be absent for the paediatric population.

Contrary to our hypothesis, HIIT was not superior to MICT or nutrition advice only for improving cardiometabolic biomarkers. Although HIIT in adults may lead to acute improvements in glycaemic control, improvements following a HIIT intervention are not superior to MICT [52]. In fact, our findings suggested that MICT may be more effective for eliciting small but significant reductions in long-term blood glucose control (HbA_{1c}) particularly when compared with nutrition advice only. While it is important to interpret these findings in light of multiple testing, the improvements may have clinical relevance. In adults, a 1% absolute increase in HbA_{1c} leads to a 21% increased risk of diabetes-related death, a 14% increased risk for myocardial infarction and a 37% increased risk for microvascular complications in adults [53]. Although subtle, the improvement observed in HbA_{1c} following 12 weeks of MICT potentially reduced the risk of cardiovascular morbidity in this group of children with obesity. The paucity of evidence supporting a dose–response relationship between exercise intensities and long-term glycaemic control in children with obesity warrants further investigation.

Last, it is important to consider adherence to exercise interventions, particularly when the eventual objective is to promote increases in long-term physical activity and exercise. We note that marginally greater attrition was seen in the HIIT intervention (30%) compared with MICT

(25%) and nutrition advice-only (21%) interventions with a 'lack of time, interest and motivation' stated most commonly. However, similar reasons were also stated in the MICT and nutrition advice only groups alongside 'dissatisfaction with group allocation' and a 'refusal to participate'. It is crucial to understand that children are strongly dependent on their parents and the aforementioned reasons likely reflect the opinion of the entire family, not just the child. To date, program completion is the only available outcome to gauge 'enjoyment' of HIIT compared with MICT in this population. While it is highly likely that affective valence towards an exercise prescription will vary depending on the individual, future research should assess this using validated scales or questionnaires. Until such evidence is available, we recommend that HIIT should be an option for children who enjoy it, but alternatives including MICT should also be on offer.

To our knowledge, this is the largest exercise training study in children with obesity comparing the effect of HIIT and MICT on CRF and VAT using gold-standard methodologies. Importantly, these findings are the first to emerge from a multicentre trial, which promotes greater generalisability. While there are limitations inherent to conducting a human trial across two continents, these differences were planned and accounted for in the statistical analysis. We also note that a considerable number of investigated outcomes had a significant association with age, but the nature of this association was not further investigated. Lastly, the inter-individual variability for abdominal adipose tissue outcomes was larger than anticipated, and may have limited our ability to detect treatment effects.

5 Conclusion

Twelve weeks of HIIT is a potent stimulus for improving CRF in children with obesity. While adiposity and cardiometabolic biomarkers were unaffected by the interventions, the cardiometabolic protection associated with increasing CRF is paramount and should be emphasised when recommending HIIT programs in paediatric obesity.

Acknowledgements The authors thank Ms Rachel Haddow for holding the nutrition consultations with participants and their families at The University of Queensland, as well as Mr. Aiman Al Najjar and Mrs. Nicole Atcheson for their magnetic resonance imaging technical support. Cardiorespiratory fitness assessments and exercise sessions were conducted at the core facility NeXt Move, Norwegian University of Science and Technology.

Compliance with Ethical Standards

Funding This work was supported by St Olav's Hospital and the Norwegian University of Science and Technology (Grant no. 9527), Sports Medicine Australia Research Foundation, and The Wesley and St Andrew's Research Institute (Grant no. 2014-01). Shelley E. Keating is supported by a National Health and Medical Research Council Early Career Fellowship.

Conflict of interest Jeff S. Coombes reports grants outside the submitted work from Coca Cola and Renew Corp and personal fees from Tolmar and Novo Nordisk Pharmaceuticals. Shelley E. Keating reports grants outside the submitted work from Exercise and Sports Science Australia and Diabetes Australia. Sjaan R. Gomersall reports grants outside the submitted work from Exercise and Sports Science Australia and Cycling Victoria. Katrin A. Dias, Charlotte B. Ingul, Arnt E. Tjonna, Turid Follestad, Mansoureh S. Hosseini, Siri M. Hollekim-Strand, Torstein B. Ro, Margrete Haram, Else Marie Huuse, Peter SW. Davies, Peter A. Cain and Gary M. Leong have no conflicts of interest directly relevant to the content of this article.

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Regional Committee for Medical and Health Research Ethics (Reference no. 2009/1313-4), The University of Queensland Human Research Ethics Committee (Reference no. 2013000539), The Mater Hospital Human Research Ethics Committee (Reference no. HREC/13/MHS/119/AM01) and the Uniting Care Health Human Research Ethics Committee (Reference no. 1324), and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

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