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John Wilding Professor of Medicine &
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Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Effect of Aerobic Exercise Intensity on Energy Expenditure and Weight Loss in Severe Obesity—A Randomized Controlled Trial

Jarle Berge [1,2,3], *Jøran Hjelmesæth* [1,4], *Jens K. Hertel* [1], *Espen Gjevestad*[1,2,5], *Milada Cvancarova Småstuen* [1], *Line Kristin Johnson*[1], *Catia Martins* [6,7], *Eivind Andersen*[8], *Jan Helgerud*[9,10], *and Øyvind Støren*[3,8]

Objective: This study aimed to compare the effects of two aerobic exercise programs of different intensities on energy expenditure.
Methods: This was a single-center randomized controlled trial of patients with severe obesity allocated to a 24-week moderate-intensity continuous training (MICT) program or a combined MICT with high-intensity interval training (HIIT/MICT) program. The primary outcome was energy expenditure during exercise (EEDE). Secondary outcomes included resting metabolic rate, cardiorespiratory fitness, and body composition.
Results: A total of 82 (56% females) patients were screened, and 71 (55% females) patients were allocated to HIIT/MICT ($n=37$) or MICT ($n=34$). Per-protocol analysis showed that EEDE increased by 10% (95% CI: 3%-17%) in the HIIT/MICT group ($n=16$) and 7.5% (95% CI: 4%-10%) in the MICT group ($n=24$), with no differences between groups. In the 8- to 16- week per-protocol analysis, the HIIT/MICT group had a significantly larger increase in EEDE compared with the MICT group. Resting metabolic rate remained unchanged in both groups. HIIT/MICT and MICT were associated with significant weight loss of 5 kg and 2 kg, respectively.
Conclusions: Patients completing a 24-week combined HIIT/MICT program did not achieve a higher EEDE compared with those who completed a 24-week MICT program. The HIIT/MICT group experienced, on average, a 3-kg-larger weight loss than the MICT group.

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Study Importance Questions

What is already known?

- Aerobic exercise increases cardiorespiratory fitness, and thus energy expenditure, during exercise.
- Regular aerobic exercise with high-intensity interval training (HIIT) improves cardiorespiratory fitness more than moderate-intensity continuous training (MICT).

What does this study add?

- Patients with severe obesity completing a 24-week combined HIIT/MICT program did not increase their energy expenditure during exercise or at rest to a greater extent than patients completing a 24-week MICT.
- Despite no specific focus on body weight, combined HIIT/MICT and MICT were associated with significant weight loss of 5 kg and 2 kg, respectively.

How might these results change the focus of clinical practice?

- Both combined HIIT/MICT and MICT may increase energy expenditure and induce a moderate weight loss, but HIIT/MICT seems to be associated with a significantly larger weight loss.
- Taking into account the high rates of withdrawals and noncompleters in the HIIT/MICT group, it might be appropriate to tailor the treatment to specific patients by informing them of the pros and cons of HIIT/MICT versus MICT.

Introduction

High cardiorespiratory fitness in people with overweight and obesity is associated with larger weight loss (1,2), lower odds of weight gain (3), reduced liver fat (4), and lower waist circumference (5). However, compared with normal-weight patients, patients with severe obesity often have reduced cardiorespiratory fitness (1) and therefore relatively lower energy expenditure during exercise (EEDE). In addition, impaired cardiorespiratory

[1] Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway. Correspondence: Jarle Berge (jarle.berge@siv.no) [2] Clinic of Medicine and Rehabilitation, Vestfold Hospital Trust, Stavern, Norway [3] Nature, Health and Environment, University of South-Eastern Norway, Bø, Norway [4] Department of Endocrinology, Morbid Obesity and Preventive Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway [5] Norwegian Police University College, Stavern, Norway [6] Obesity Research Group, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway [7] Center for Obesity, Department of Surgery, St. Olav Hospital, Trondheim University Hospital, Trondheim, Norway [8] Department of Sport, Physical Education and Outdoor Life Studies, University of South-Eastern Norway, Bø, Norway [9] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway [10] Myworkout, Medical Rehabilitation Clinic, Trondheim, Norway.

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fitness may also be associated with lower resting metabolic rate (RMR) in patients with obesity (6,7).

There is a well-known association between EEDE and cardiorespiratory fitness, measured as maximum volume of oxygen consumed (VO_{2max}), as VO_{2max} defines the potential for EEDE (8). Aerobic exercise with both high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) has been performed as intervention exercise training in studies including both persons with normal weight and those with obesity (9-12). However, previous studies have reported a larger increase in VO_{2max} after HIIT than after MICT (9,13,14). Furthermore, the medium- to long-term effects of exercise programs of varying intensity on EEDE and energy expenditure during rest in patients with severe obesity are uncertain.

In light of this, the aim of the present randomized controlled trial including patients with severe obesity was to compare the effects of two different 24-week aerobic exercise programs of varying intensity on EEDE, RMR, and VO_{2max}. Our primary hypothesis was that patients completing a 24-week combined HIIT/MICT program would increase their EEDE and RMR to a greater extent than patients completing a clean 24-week MICT program.

Methods

Study design and location

This was an open-label, randomized, single-center trial conducted at the Morbid Obesity Centre, Vestfold Hospital Trust in Tønsberg, Norway. Consecutive patients referred to the outpatient clinic were initially prescreened by the clinicians (staff). Patients who were willing to consider participation and to postpone the planned specific weight loss treatment were informed about the study by telephone, and those who showed interest underwent a second medical screening at the center.

First, to gradually prepare patients for increasing physical activity and to prevent injuries, all patients initially underwent 8-week MICT. Second, completers were randomized and allocated (1:1 ratio) to either 8-week HIIT or 8-week MICT. Third, both groups subsequently underwent 8-week MICT (Figure 1), making it possible to investigate any legacy effects. Patients were instructed to maintain their habitual dietary intakes during the intervention, with no specific focus on weight loss. Data were collected between January 5, 2015, and June 9, 2017.

Patients

Adult (≥18 years) patients with severe obesity (BMI ≥ 40.0 $kg * m^{-2}$ or 35.0-39.9 $kg * m^{-2}$ with at least one obesity-related comorbidity) and a stable body weight during the last 3 months (±5 kg) were deemed eligible. Exclusion criteria were ascertained by qualified health personnel and included uncompensated heart failure, recent myocardial infarction, or stroke during the last 6 months, severe arrhythmia or heart failure, unstable angina pectoris, renal failure, pregnancy, severe eating disorders, active substance abuse, being on a standardized diet, taking medications known to significantly affect appetite or metabolism, and physical immobility. Written informed consent was obtained from all patients. The study was approved by the Regional Committees for Medical and Health Research Ethics South East Norway (2013/1849) and was registered at ClinicalTrials.gov (identifier NCT02311738).

Exercise intervention

All patients were prescribed three consecutive 8-week workout programs including three workouts per week, and both groups were prescribed MICT during the first and the third 8-week program (Figure 1). The MICT consisted of a 10-minute warm-up at 50% of heart rate maximum (HR_{max}) (±3 beats per minute [BPM]), a 35-minute exercise at 70% of HR_{max} (±3 BPM), and a 4-minute cooldown at 50% of HR_{max} (±3 BPM). The HIIT consisted of a 10-minute warm-up at 70% of HR_{max} (±3 BPM), then 4 * 4 minutes at 90% to 95% of HR_{max} divided by 3-minute active recovery periods at 70% of HR_{max} (±3 BPM), and finally a 5-minute cooldown at 70% of HR_{max} (±3 BPM). The mechanical work was continuously adjusted in order to match the targeted heart rate (HR) zones. The total time for each of the exercise durations was 49 minutes for MICT and 40 minutes for HIIT, and the protocols were isocaloric at baseline (mean 485 kcal).

One of three sessions per week was a group session (maximum 12 patients in each group) on ergometer bikes led by the project manager (JB). The two remaining weekly sessions were performed individually, either cycling or walking/running. HR monitors (Polar A300 and Polar WearLink + H7 Bluetooth; Polar Electro Oy, Kempele, Finland) were provided to all patients for intensity control. All sessions and time in HR zone were collected and registered. To minimize dropout, all patients were assigned their own individual advisor who provided motivation and followed them up during the course of the program. In addition, three times per week during the intervention, the patients received an exercise reminder by mail, and the patients had to provide feedback when the sessions were completed.

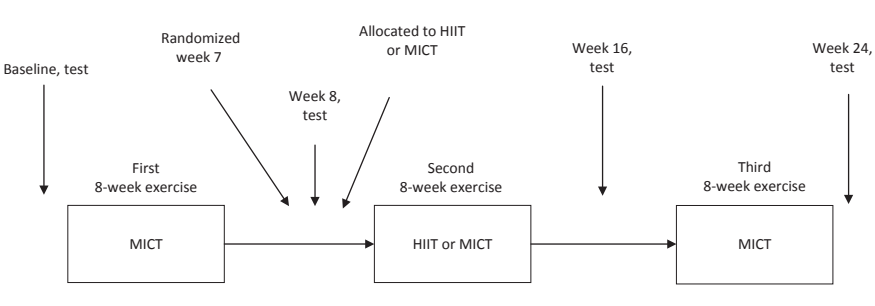

Figure 1 Timeline for visit and training. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training.

Outcomes

The primary outcome was the 24-week change in EEDE, and the prespecified secondary outcomes were 24-week changes in RMR, VO_{2max}, body weight, BMI, waist circumference, fat-free mass (FFM), and fat mass. Exploratory outcomes were changes in energy expenditure in EEDE and RMR adjusted for various measures of body composition, daily activity, daily total energy intake, and appetite control.

Measurements

EEDE, RMR, and VO_{2max} tests, as well as body weight and body composition measurements, were performed at baseline and week 8, 16, and 24 (Figure 1). Measurements of activity during free living and registration of food frequency questionnaire were performed at week −1 and 23. Appetite control was assessed at baseline, week 16, and week 24.

Ergo-spirometry. EEDE, RMR, and VO_{2max} were performed at the same day to keep the number of test days as low as possible. EEDE, RMR, and VO_{2max} were measured by use of Metalyser, Cortex 2 (Biophysik, Leipzig, Germany). The system was equipped with a mixing chamber with oxygen (O_2) and carbon dioxide (CO_2), and the ventilation was analyzed continuously. Volume of oxygen consumed (VO_2) measures were used to calculate energy expenditure, corrected for respiratory exchange ratio, based on the formula from Zuntz (8). These measures were used to calculate RMR and EEDE (42). Before each ergo-spirometry test, the device was calibrated with room air (23°C) at 20.93% O_2 and 0.03% CO_2 and a certified gas containing 15.80% O_2 and 4.98% CO_2. The calibration of ventilatory volume was conducted with a manual three-liter syringe (Hans Rudolph, Shawnee, Kansas). Barometric pressure was calibrated with an electronic barometer (GB3300) (Greisinger Electronic GmbH, Regenstauf, Germany). A face mask (Hans Rudolph V2, Shawnee, Kansas) with different sizes (Petit, Extra-Small, Small, Medium) was used to collect expired air during the tests. HR was measured every 5 seconds with Polar WearLink + H7 Bluetooth and Polar A300.

VO_{2max}. VO_{2max} (15) was expressed as liters per minute ($L*min^{-1}$) and calculated per kilogram of body weight ($mL*kg^{-1}*min^{-1}$) (15) and body weight raised to the power of 0.75 ($mL*kg^{-0.75}*min^{-1}$) (16-19). The VO_{2max} test was performed as an individualized incremental treadmill test on a Woodway PPS 55 Plus (WOODWAY GmbH, Weil am Rhein, Germany). The velocity was increased alternately by 0.5 $km*h^{-1}$, or the inclination by 1% every 30 seconds until voluntary exhaustion. The duration of the tests ranged from 4 to 10 minutes. Voluntary exhaustion, respiratory exchange ratio ≥ 1.05, HR ≥ 95% of HR_{max}, Borg scale ≥ 17, and a flattening of the VO_2 curve (< 1 mL/min) were used to evaluate whether VO_{2max} had been achieved. VO_{2max} was calculated as the highest of three consecutive 10-second measurements (total 30 s). HR_{max} was set as the highest observed value during the test, + 3 beats (20,21).

EEDE. EEDE testing was performed on the same day (70-90 min after the VO_{2max} test) on the same treadmill, at 70% of VO_{2max}. The velocity or inclination was adjusted to reach the target intensity based on the VO_{2max} test earlier that same day. The duration of the tests ranged from 5 to 10 minutes, to ensure a minimum of 3 minutes' steady state at 70% VO_{2max}. EEDE was expressed as the absolute energy expenditure in $kcal*h^{-1}$.

RMR. RMR was measured in a fasted state and after at least 48 hours without exercise to exclude excess postexercise oxygen consumption (EPOC). After a 1-hour rest in the fasted state, RMR was measured with the patient lying relaxed at 45° in a chair in a dark, quiet room for 30 minutes. The exhaled air was analyzed continuously every 10 seconds through a facemask. The criteria used to accept a test as valid are whether steady state is achieved (10% or less coefficient of variation in VO_2/validation of CO_2 production) and whether the patients does not fall asleep (22). The data were calculated from a 15-minute period during the middle of the test (−5 min at start and −10 min at end) (22,23). RMR was expressed as the absolute energy expenditure in $kcal*d^{-1}$.

Energy expenditure related to body mass during exercise and adjusted RMR. EEDE and RMR were calculated as energy expenditure related to kilogram ($kcal*kg^{-1}$) and FFM ($kcal*FFM^{-1}$) and scaled to body weight ($kcal*kg^{-0.75}$ or $kcal*kg^{-0.67}$) (8,23,24). In addition, adjusted metabolic rates for each individual during exercise and rest were calculated as suggested by Ravussin and Bogardus (25): adjusted metabolic rate = group mean metabolic rate plus measured metabolic rate minus the predicted metabolic rate. Furthermore, linear regression equations for predicting metabolic rates were obtained from the baseline population ($N = 40$) (25):

$$\text{EEDE}(\text{kcal}*\text{h}^{-1}) = 14.3 \times \text{FFM}(\text{kg}) + (-371.4)$$

$$\text{RMR}(\text{kcal}*\text{d}^{-1}) = 25.7 \times \text{FFM}(\text{kg}) + 771.4$$

Metabolic adaptation was calculated as the difference between measured and predicted metabolic rates.

Anthropometrics and body composition measures. Body weight and body composition were measured with patients wearing light clothing and no shoes using the bioelectrical impedance analyzer Tanita BC-418 (Tokyo, Japan). Height was measured to the nearest 0.1 cm using Soehnle (Backnang, Germany) professional wall-mounted measuring tape. BMI was calculated as weight in kilograms divided by height in meters squared ($kg*m^{-2}$). Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower margin of the lowest rib and the top of the iliac crest in the horizontal plane.

Activity during free living. Measurements of 24-hour activity during free living were performed with accelerometer (ActiGraph wGT3x-BT, Pensacola, Florida) on the wrist. The 24-hour activity was expressed as daily activity counts per minute (vector magnitude). The patients were instructed to wear the accelerometer for 24 hours during 7 days, including the weekend. Minimum thresholds of valid data were set to both 4 days and 10 hours per day (26).

Diet. Patients were asked to maintain the same diet before each visit and were given a standardized breakfast/lunch (591 kcal, 19% protein, 45% carbohydrate, and 35% fat) to

minimize the effect of various food intakes on measurements. Patients had at least 2 hours' rest between the RMR and VO_{2max} test, and the breakfast/lunch was provided immediately after the RMR test.

Food frequency questionnaire. Patients completed a food frequency questionnaire and were asked to register their habitual dietary intake at the time of measurement. A 180-item food frequency questionnaire developed in Norway and validated to assess habitual diet intake among men and women (27,28) was used. The dietary data were entered by scanning using the Teleform Program (version 10.0) (Datascan, Oslo, Norway). Daily intake of foods, energy, and nutrients were calculated using software (KBS version 7.3 2017) developed at the Institute of Basic Medical Sciences, University of Oslo. The software is based on the Norwegian Food Composition Table (29).

Appetite control. Subjective feelings of appetite (hunger, desire to eat, prospective food consumption, and fullness) were assessed during fasting and every 30 minutes after a standardized breakfast (for a period of 3 h) using visual analogue scales (30).

Sample size

Based on VO_{2max} from previous research (10,11,13,31), we estimated a mean increase in energy expenditure of 7.5% and 15% per hour during exercise after MICT and HIIT, respectively, with a common SD of 4. With a significance level of 5% and achieving a power > 80%, we would need 17 individuals in each group to complete the study. Allowing for a dropout rate of 30%, we would need at least 22 patients in each group.

Randomization

Anticipating a relatively high initial dropout rate, randomization was performed at the end of week 7. Patients completing the first 7 weeks were stratified into two groups, either above or below baseline median VO_{2max}, and subsequently block-randomized into either the MICT or the HIIT/MICT group using block sizes of 4. The randomization was performed by the study biostatistician (MCS) using Stata software (version 14.2; StataCorp, College Station, Texas).

Statistical analyses

All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, New York). Descriptive statistics are presented as mean (SD) unless otherwise specified. Outcome measures collected over time were analyzed using a linear mixed model with an unstructured correlation matrix to account for dependencies, as the same individuals were measured several times. Baseline data from all randomly assigned patients were included in both the per-protocol and intention-to-treat principle analyses, with treatment, time, and treatment–time interaction entered as the fixed effects. The per-protocol analyses were performed by excluding patients who withdrew, discontinued intervention, and/or attended fewer than 70% of prescribed exercise sessions (17 of 24 sessions per 8 weeks) from randomization to the end of treatment. The latter is in accordance with previous studies considering 70% to 80% adherence as per protocol (14,20,21). $P < 0.05$ was considered statistically significant. No correction for multiple testing was performed, and except for the primary outcome, the study results should be considered exploratory.

Results

A total of 665 (64% females) consecutive patients referred to the obesity outpatient clinic were initially prescreened by clinicians (staff), but the majority were ineligible because they were not willing to postpone the planned specific weight loss treatment. However, 119 (53% females) eligible patients were informed about the study, and 82 (56% females) patients underwent medical screening and agreed to participate. Before baseline, 11 patients withdrew consent, leaving 71 (55% females) patients who completed the first 8 weeks of the program and who were randomized and allocated to either 16 weeks of MICT ($n = 34$) or 8 weeks of HIIT followed by 8 weeks of MICT ($n = 37$) (Figure 2). A total of 21 randomized patients (30%) were lost to follow-up, and additionally, 10 patients (14%) attending the 24-week follow-up did not complete at least 70% of the prescribed exercise sessions (Figure 2, Supporting Information Table S1), leaving 40 patients to be included in the per-protocol analysis (MICT group, $n = 24$; HIIT/MICT group, $n = 16$).

The 71 randomized patients (55% females) had a baseline mean (SD) age of 43.8 (11.3) years, BMI 41.9 (5.3) $kg * m^{-2}$, body weight 123.3 (22.2) kg, EEDE 649 (155) $kcal * h^{-1}$, RMR 2,500 (490) $kcal * d^{-1}$, and VO_{2max} 3.10 (0.70) $L * min^{-1}$. Baseline characteristics did not differ significantly between groups except for a lower self-reported daily calorie intake ($P = 0.027$) in the HIIT/MICT group compared with the MICT group (Table 1).

Baseline characteristics between completers and noncompleters did not differ significantly except for body weight in the HIIT/MICT group (Supporting Information Table S1).

Primary outcome

In the per-protocol analysis, EEDE increased in both the HIIT/MICT group and the MICT group, with a mean change of 67 (95% CI: 19 to 118) $kcal * h^{-1}$ (10.4%) in the HIIT/MICT group and 52 (95% CI: 27 to 77) $kcal * h^{-1}$ (7.5%) in the MICT group, with no significant difference between groups (Table 2, Figure 3). The intention-to-treat analyses showed increased EEDE in the MICT group but not in the HIIT/MICT group, with no significant difference between groups (Supporting Information Table S2).

Secondary outcomes

In the per-protocol analysis, RMR did not change significantly, with no difference between groups (Table 2, Figure 4). VO_{2max} increased in both the HIIT/MICT and the MICT group, with a mean change of 0.30 (95% CI: 0.10 to 0.50) $L * min^{-1}$ (9.7%) and 0.30 (95% CI: 0.22 to 0.38) $L * min^{-1}$ (9.1%), respectively, with no significant between-group difference (Table 2, Figure 5). BMI, body weight, and fat mass decreased significantly more in the HIIT/MICT group than in the MICT group, with a between-group difference of −1.2 (95% CI: −2.3 to −0.2) kg/m^2, −3.3 (95% CI: −6.4 to −0.2) kg, and −2.9 (95% CI: −5.3 to −0.5) kg, respectively (Table 2). Waist circumference decreased similarly in both groups, whereas FFM remained

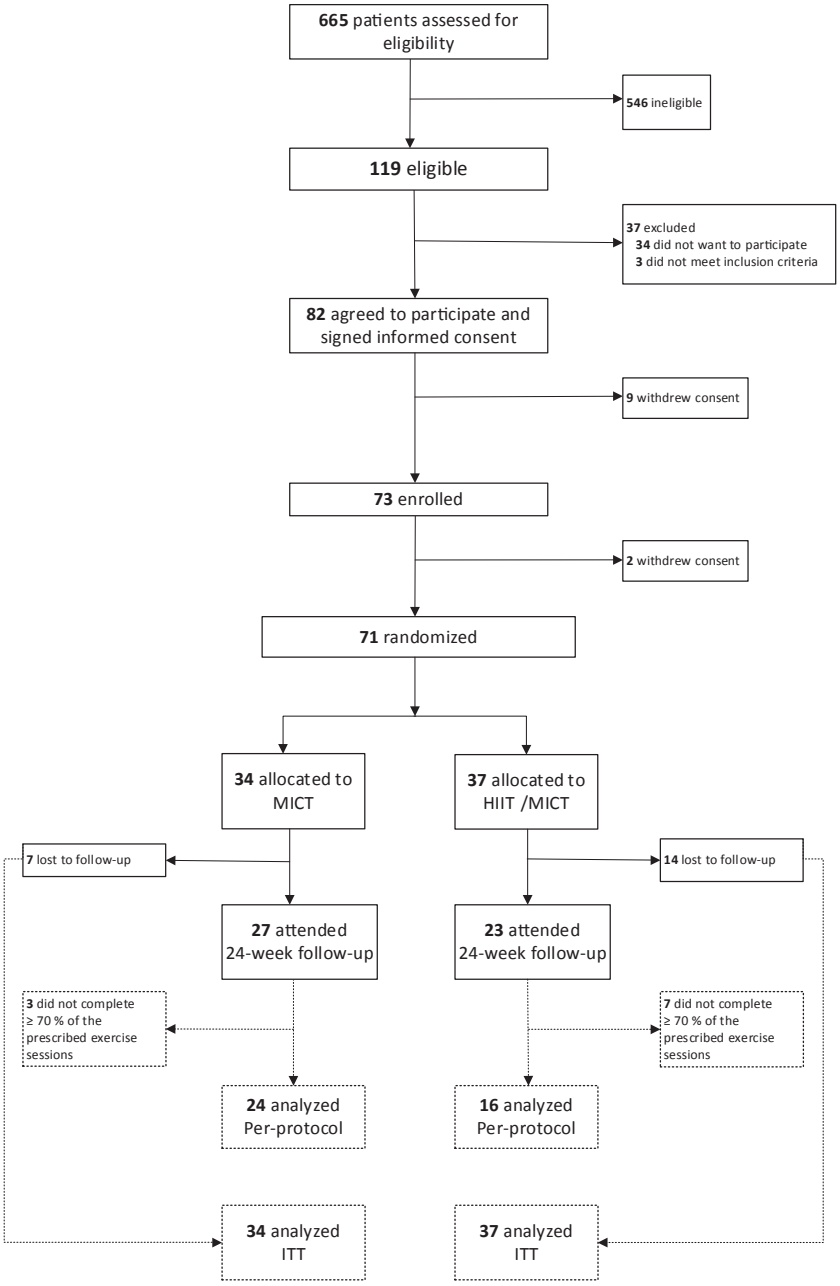

Figure 2 Flowchart. HIIT, high-intensity interval training; ITT, intention-to-treat principle; MICT, moderate-intensity continuous training.

stable in both groups (Table 2). The results from intention-to-treat analyses were comparable to those from the per-protocol analyses (Supporting Information Table S2).

Changes in primary and secondary outcomes between 8-, 16-, and 24-week follow-up

In the 8- to 16-week per-protocol analysis, the HIIT/MICT group had a significantly larger increase in EEDE compared with the MICT group, with a between-group difference of 36.5 (95% CI: 6.4 to 66.5) kcal * h^{-1} (Table 2, Figure 3). RMR declined significantly between 8- and 16-week follow-up in the HIIT/MICT group only but increased between 16- and 24-week follow-up, with no significant between-group difference (Table 2, Supporting Information Table S3, Figure 4).

Energy expenditure related to FFM, baseline to 24-week follow-up

RMR per kilogram FFM did not change significantly during the study (Supporting Information Table S3). EEDE per kilogram FFM

TABLE 1 Baseline characteristics

	MICT group ($n=34$)	HIIT/MICT group ($n=37$)
Sex		
Female	19 (56%)	20 (54%)
Male	15 (44%)	17 (46%)
Age (y)	44.2 (9.8)	43.3 (12.6)
White ethnicity	31 (91.2%)	37 (100%)
Anthropometric		
Body weight (kg)	127 (23.9)	120 (20.2)
BMI ($kg*m^{-2}$)	42.8 (5.3)	41.1 (5.1)
Waist circumference (cm)	123 (15.3)	119 (11.0)
Fat-free mass (kg)	70.1 (17.3)	68.0 (14.9)
Fat mass (kg)	56.8 (13.0)	51.7 (12.2)
Energy expenditure		
Energy expenditure during exercise ($kcal*h^{-1}$)	665 (166)	642 (145)
Resting metabolic rate ($kcal*d^{-1}$)	2,463 (492)	2,535 (492)
Cardiorespiratory fitness		
VO_{2max} ($L*min^{-1}$)	3.20 (0.70)	3.10 (0.70)
VO_{2max} ($mL*kg^{-1}*min^{-1}$)	25.1 (4.1)	25.9 (4.8)
Energy balance		
Daily activity (CPM)[○]	1,707 (467)	1,609 (580)
Daily total energy intake ($kcal*d^{-1}$)[#]	2,890 (877)	2,383 (969)

Data presented as numbers (%) or mean (SD).
CPM, counts per minute; VO_{2max}, maximum volume of oxygen consumed.
[○]$n=34$ MICT group and 33 HIIT/MICT group.
[#]$n=32$ MICT group and 37 HIIT/MICT group.

increased significantly in both groups, with no between-group differences (Supporting Information Table S3). However, EEDE adjusted for FFM (via linear regression analysis) increased similarly in both groups, by 17% in the HIIT/MICT group and 15% in the MICT group, slightly more than the 10% versus 8% increase in EEDE without adjusting for FFM. Furthermore, the adjusted RMR did not change significantly in either group. To conclude, the results after adjustments by FFM via linear regression analysis were in line with our main findings as measured by indirect calorimetry (Supporting Information Table S4). No significant metabolic adaptation after the completion of the two treatment programs was found (Supporting Information Table S4).

Daily activity and total energy intake, week −1 to week 23. In the per-protocol analysis, daily activity and total energy intake or macronutrient distribution did not change significantly from week −1 to week 23 in either group (Table 2, Supporting Information Table S5). The intention-to-treat analyses showed no differences between groups (Supporting Information Table S2).

Appetite, baseline to 24-week follow-up. In the per-protocol analyses, no significant difference between groups (area under curve) were seen for any of the subjective feelings of appetite (Supporting Information Table S3).

Discussion

Brief synopsis of key findings

In contrast with our hypothesis, treatment-seeking patients with severe obesity who completed at least 70% of the prescribed isocaloric exercise sessions of a 24-week combined MICT/HIIT program did not increase EEDE to a greater extent than those who completed a 24-week MICT program, with RMR remaining unchanged in both groups. Although the patients were specifically advised not to focus on weight loss, body weight was reduced by approximately 2 kg and 5 kg in the MICT and HIIT/MICT group, respectively.

EEDE and VO_{2max}

EEDE and VO_{2max} increased similarly (Figures 3 and 5) in the MICT group (7.5% and 9.1%, respectively) and in the HIIT/MICT group (10.4% and 9.7%, respectively) during the 24-week follow-up. This is in accordance with the well-known association between EEDE and VO_{2max}, as VO_{2max} defines the potential for EEDE (8). Furthermore, our finding that 8 weeks of HIIT (week 8 to week 16) increased VO_{2max} and EDEE to a larger extent than 8 weeks of MICT is supported by previous studies (9-11) showing HIIT to be more efficient than MICT at improving VO_{2max}.

Clinically significant weight losses (2-5 kg) were demonstrated in both groups after 24-week follow-up (Table 2). The energy intake and everyday activity level were, however, unchanged in both groups (Table 2). Because energy intake was self-reported, it must be interpreted with caution (32). It might be speculated that the weight loss in both groups may be partly explained by the increased EEDE at each exercise session, since weight loss following exercise is mainly related to the acute energy expended driven by each exercise bout (33).

RMR

Our finding that RMR did not change significantly during the intervention (Figure 4, Table 2, Supporting Information Table S3) is in line with the results of a recent systematic review and meta-analysis evaluating the effect of different exercise methods on RMR (34). However, we measured RMR more than 48 hours after exercise to prevent bias from EPOC and therefore might have missed a temporary increased RMR during this period (35). Furthermore, because exercise intensity is a major determinant of EPOC (36), and because a higher EPOC has been reported after HIIT compared with MICT in previous studies (37,38), we speculate that HIIT might have increased EPOC more than MICT in the present study. Unfortunately, EPOC was not assessed in the present study.

In addition, RMR per kilogram of body weight increased in both the HIIT/MICT and MICT group, but no changes were observed in RMR per kilogram of FFM (Supporting Information Table S3). Taking into account that FFM is a key determinant of RMR, and that FFM did not change significantly during the interventions, the latter finding may partly explain the stable RMR in both groups as well as the increase in RMR per kilogram of body weight (33,34,39). Furthermore, our results are supported by previous evidence demonstrating that weight loss caused by aerobic exercise preserves both FFM (33) and RMR (40).

TABLE 2 Primary, secondary and exploratory outcomes, per-protocol analyses

	MICT group	*P* value within group	HIIT/MICT group	*P* value within group	Between-group differences (95% CI)	*P* value between group
Primary outcome						
*Energy expenditure during exercise (kcal * h^{-1})*	(*n*=24)		(*n*=16)			
Baseline	690 (620 to 761)	-	642 (576 to 709)	-	47.9 (–51.0 to 146.7)	0.333
8 weeks	708 (647 to 768)	-	653 (573 to 709)	-	54.1 (–41.2 to 149.5)	0.258
16 weeks	714 (651 to 777)	-	696 (612 to 781)	-	17.7 (–82.6 to 117.9)	0.723
24 weeks	742 (681 to 803)	-	709 (625 to 797)	-	33.3 (–64.1 to 130.6)	0.493
Change from baseline to 24 weeks	52.0 (26.6 to 77.3)	<0.001	66.7 (18.7 to 118)	0.012	–14.7 (–31.9 to 61.2)	0.527
Percent change	7.5	-	10.4	-	-	-
Change from 8 to 16 weeks	6.6 (–14.1 to 27.2)	0.516	43.1 (21.1 to 65.0)	0.001	–36.5 (6.4 to 66.5)	0.019
Percent change	0.9	-	6.6	-	-	-
Secondary outcomes						
*Resting metabolic rate (kcal * d^{-1})*	(*n*=24)		(*n*=16)			
Baseline	2,541 (2,346 to 2735)	-	2,407 (2,225 to 2,588)	-	134 (–139 to 406)	0.327
8 weeks	2,527 (2,337 to 2718)	-	2,388 (2,154 to 2621)	-	140 (–162 to 441)	0.355
16 weeks	2,463 (2,248 to 2679)	-	2,303 (2039 to 2568)	-	160 (–181 to 501)	0.348
24 weeks	2,572 (2,353 to 2791)	-	2,445 (2,219 to 2675)	-	127 (–189 to 442)	0.421
Change from baseline to 24 weeks	31.3 (–44.3 to 107)	0.401	38.1 (–102 to 182)	0.555	–6.8 (–135 to 149)	0.921
Percent change	1.2	-	1.6	-	-	-
Change from 8 to 16 weeks	–64.0 (–182 to 53.4)	0.271	–84.5 (–160 to –8.9)	0.031	20.4 (–173 to 133)	0.788
Percent change	2.5	-	3.5	-	-	-
*Cardiorespiratory fitness (VO_{2max}, L * min^{-1})*	(*n*=24)		(*n*=16)			
Baseline	3.31 (3.00 to 3.62)	-	3.07 (2.77 to 3.37)	-	0.24 (–0.21 to 0.68)	0.286
8 weeks	3.45 (3.16 to 3.74)	-	3.16 (2.80 to 3.51)	-	0.29 (–0.15 to 0.74)	0.191
16 weeks	3.46 (3.16 to 3.76)	-	3.29 (2.95 to 3.65)	-	0.16 (–0.29 to 0.61)	0.481
24 weeks	3.60 (3.32 to 3.89)	-	3.37 (2.98 to 3.76)	-	0.25 (–0.19 to 0.70)	0.255
Change from baseline to 24 weeks	0.30 (0.22 to 0.38)	<0.001	0.30 (0.10 to 0.50)	0.007	–0.02 (–0.19 to 0.15)	0.830
Percent change	9.1	-	9.7	-	-	-
Change from 8 to 16 weeks	0.01 (–0.07 to 0.08)	0.809	0.13 (0.05 to 0.24)	0.006	–0.14 (0.02 to 0.25)	0.023
Percent change	0.3	-	4.1	-	-	-
*BMI (kg * m^{-2})*	(*n*=24)		(*n*=16)			
Baseline	42.0 (40.4 to 43.6)	-	39.6 (36.9 to 42.4)	-	2.4 (–0.5 to 5.2)	0.101
8 weeks	41.3 (39.7 to 43.0)	-	38.9 (36.2 to 41.7)	-	2.4 (–0.5 to 5.3)	0.101
16 weeks	41.4 (39.7 to 43.1)	-	38.2 (35.4 to 41.0)	-	3.1 (0.2 to 6.1)	0.038
24 weeks	41.3 (39.6 to 43.1)	-	37.7 (34.8 to 40.6)	-	3.6 (0.6 to 6.7)	0.022

(continues)

TABLE 2 (continued).

	MICT group	*P* value within group	HIIT/MICT group	*P* value within group	Between-group differences (95% CI)	*P* value between group
Change from baseline to 24 weeks	−0.7 (−1.3 to −0.1)	0.033	−1.9 (−2.9 to −1.0)	0.001	1.2 (−2.3 to −0.2)	0.019
Percent change	1.7	-	4.8	-	-	-
Change from 8 to 16 weeks	0.0 (−0.2 to 0.3)	0.871	−0.7 (−1.1 to −0.3)	0.001	0.7 (−1.2 to −0.3)	0.001
Percent change	0.2	-	1.8	-	-	-
Body weight (kg)	(*n*=24)		(*n*=16)			
Baseline	127 (119 to 135)	-	111 (102 to 120)	-	16.1 (4.2 to 28.0)	0.009
8 weeks	125 (117 to 134)	-	109 (100 to 118)	-	16.0 (4.1 to 28.0)	0.010
16 weeks	126 (117 to 134)	-	107 (98.2 to 117)	-	18.1 (5.9 to 30.3)	0.005
24 weeks	125 (117 to 135)	-	106 (96.4 to 115)	-	19.4 (7.2 to 31.7)	0.003
Change from baseline to 24 weeks	−2.1 (−4.8 to −0.1)	0.040	−5.4 (−8.0 to −2.8)	<0.001	3.3 (−6.4 to −0.2)	0.036
Percent change	1.7	-	4.9	-	-	-
Change from 8 to 16 weeks	−0.1 (−0.7 to 0.9)	0.858	−2.0 (−3.1 to −0.9)	0.002	1.9 (−3.4 to −0.8)	0.002
Percent change	0.1	-	1.8	-	-	-
Waist circumference (cm)	(*n*=24)		(*n*=16)			
Baseline	123 (118 to 129)	-	115 (110 to 121)	-	7.7 (−0.2 to 15.7)	0.057
8 weeks	120 (115 to 125)	-	113.3 (107.9 to 118.8)	-	6.6 (−0.9 to 14.1)	0.082
16 weeks	119 (114 to 124)	-	110.3 (104.2 to 116.4)	-	8.4 (0.6 to 16.2)	0.036
24 weeks	118 (112 to 123)	-	108 (102 to 114)	-	9.6 (1.7 to 17.6)	0.019
Change from baseline to 24 weeks	−5.5 (−7.0 to −4.0)	<0.001	−7.4 (−10.1 to −4.8)	<0.001	1.9 (−4.7 to 0.9)	0.169
Percent change	4.5	-	6.4	-	-	-
Change from 8 to 16 weeks	−1.2 (−1.9 to −0.6)	0.001	−3.0 (−4.5 to −1.6)	0.001	1.8 (−3.2 to −0.4)	0.011
Percent change	1.0	-	2.6	-	-	-
Fat-free mass (kg)	(*n*=24)		(*n*=16)			
Baseline	73.1 (65.9 to 80.4)	-	62.9 (56.9 to 68.8)	-	10.3 (0.4 to 20.2)	0.042
8 weeks	72.7 (65.8 to 79.7)	-	62.3 (56.5 to 68.2)	-	10.4 (0.9 to 19.9)	0.033
16 weeks	73.5 (66.6 to 80.4)	-	60.3 (53.0 to 67.7)	-	13.2 (3.2 to 23.2)	0.111
24 weeks	73.1 (66.1 to 80.2)	-	62.0 (55.8 to 68.3)	-	11.2 (1.5 to 20.9)	0.025
Change from baseline to 24 weeks	0.0 (−1.5 to 1.5)	0.928	−0.9 (−1.8 to 0.3)	0.137	0.9 (−2.9 to 1.1)	0.359
Percent change	0.0	-	1.4	-	-	-
Change from 8 to 16 weeks	0.8 (0.1 to 1.4)	0.031	−2.0 (−6.7 to 2.7)	0.378	2.8 (−6.5 to 0.9)	0.140
Percent change	1.1	-	3.2	-	-	-
Fat mass (kg)	(*n*=24)		(n=16)			
Baseline	53.8 (50.2 to 57.5)	-	48.4 (42.5 to 54.3)	-	5.4 (−0.9 to 11.8)	0.093
8 weeks	52.7 (48.8 to 56.5)	-	47.1 (41.3 to 52.8)	-	5.6 (−0.8 to 12.0)	0.084
16 weeks	52.0 (47.9 to 56.0)	-	44.4 (38.3 to 50.5)	-	7.6 (0.8 to 14.3)	0.030
24 weeks	52.1 (48.0 to 56.2)	-	43.8 (37.5 to 50.1)	-	8.3 (1.4 to 15.2)	0.020

(continues)

TABLE 2 (continued).

	MICT group	*P* value within group	HIIT/MICT group	*P* value within group	Between-group differences (95% CI)	*P* value between group
Change from baseline to 24 weeks	−1.7 (−3.3 to −0.2)	0.027	−4.6 (−6.6 to −2.6)	<0.001	2.9 (−5.3 to −0.5)	0.021
Percent change	3.2	-	9.5	-	-	-
Change from 8 to 16 weeks	−0.7 (−1.5 to 0.1)	0.097	−2.7 (−4.1 to −1.2)	0.001	2.0 (−3.4 to −0.4)	0.012
Percent change	1.3	-	5.7	-	-	-
Exploratory outcomes						
Daily activity (CPM)	(*n*=18)		(*n*=13)			
Week −1	1,650 (1,394 to 1905)	-	1992 (1598,2387)	-	−342 (−828 to 85.5)	0.107
Week 23	1,536.7 (1319,1754)		1980.7 (1,711 to 2250)		−444 (−770 to −118)	0.010
Change from baseline to 24 weeks	−113 (−299 to 73.2)	0.217	−11.5 (−343 to 320)	0.941	−101 (−265 to 468)	0.569
Percent change	3.2	-	0.6	-	-	-
*Daily total energy intake (kcal * d^{-1})*	(*n*=18)		(*n*=13)			
Week −1	2,700 (2,418 to 2981)		2037 (1,439 to 2635)		662 (892 to 1,236)	0.025
Week 23	2,618 (2,284 to 2961)		1,728 (1,516 to 1940)		890 (476 to 1,304)	<0.001
Change from baseline to 24 weeks	−81.3 (−442 to 287)	0.660	−309 (−833 to 216)	0.224	228 (−812 to 356)	0.432
Percent change	3.0		15.2			

CPM, counts per minute.

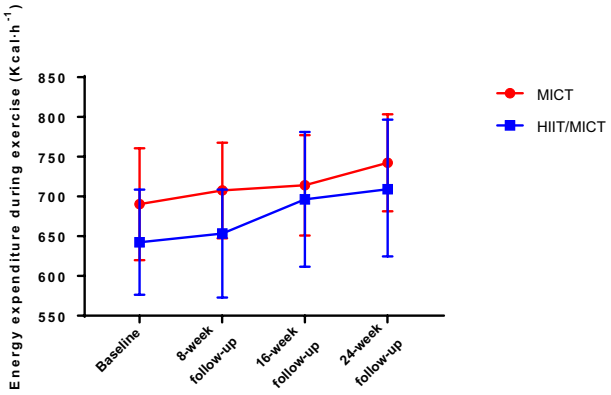

Figure 3 Energy expenditure during exercise (kcal*h^{-1}) by exercise group at baseline and at 8-week, 16-week, and 24-week follow-up. Values are presented as estimated means (95% CI) (per-protocol). Moderate-intensity continuous training (MICT) group in red dots and combined high-intensity interval training and moderate-intensity continuous training (HIIT/MICT) group in blue squares. [Color figure can be viewed at wileyonlinelibrary.com]

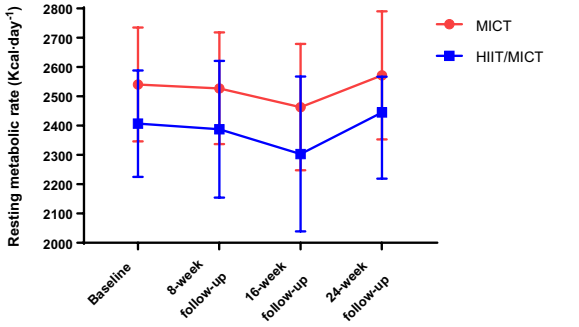

Figure 4 Resting metabolic rate (kcal*d^{-1}) by exercise group at baseline and at 8-week, 16-week, and 24- week follow-up. Value are presented as estimated means (95% CI) (per-protocol). Moderate-intensity continuous training (MICT) group in red dots and combined high-intensity interval training and moderate-intensity continuous training (HIIT/MICT) group in blue squares. [Color figure can be viewed at wileyonlinelibrary.com]

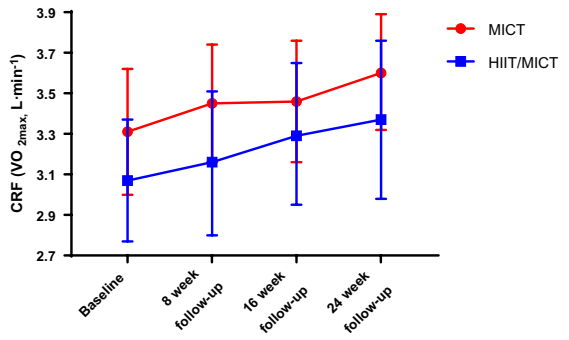

Figure 5 Maximum volume of oxygen consumed (VO_{2max}; L*min^{-1}) by exercise group at baseline and at 8-week, 16-week, and 24-week follow-up. Values are presented as estimated means (95% CI) (per-protocol). Moderate-intensity continuous training (MICT) group in red dots and combined high-intensity interval training and moderate-intensity continuous training (HIIT/MICT) group in blue squares. [Color figure can be viewed at wileyonlinelibrary.com]

Strengths and limitations

This study is strengthened by its randomized controlled design, and the generally accepted and validated methodology measuring energy expenditure. However, both the selection of participants who were particularly motivated to increase physical activity before undergoing a conventional weight loss program as well as the relatively large dropout rate (although common in this kind of study) (9,14,41,42) reduce the generalizability of our results.

The study was designed to compare the 24-week effects of a traditional MICT program with an experimental combined MICT/HIIT program, which might be judged as both a strength and a limitation. The study design allowed us to test our primary hypothesis, the overall 24-week effects of the programs, whereas the measured effects immediately after each of the three 8-week periods should be considered exploratory.

Because the study aimed to investigate the potentially different effects of exercise programs of varying intensity on physiological measures of energy expenditure, the primary analyses included patients who completed the prescribed programs (per-protocol analysis). Notably, both the retention rate and the proportion of patients who completed the prescribed exercise program were considerably lower in the HIIT/MICT group than MICT, which might have biased the results (Figure 2). However, to minimize the bias of the observed different retention rates between groups during the study, we increased the sample size from 44 (estimated) to 73 (actual). Regardless, intention-to-treat analyses (mixed models) showed similar results, supporting the per-protocol results.

Regarding test validity, we cannot rule out the possibility that the submaximal EEDE test may have been affected by the preceding VO_{2max} test. However, this potential bias was similar in both groups over time, and it has probably not significantly affected the between-group differences in the primary outcome.

Only treatment-seeking, predominantly white patients with severe obesity who were motivated and able to implement exercise over time were included in the study, thus limiting the generalizability to other populations.

Conclusion

Patients with severe obesity who completed a 24-week HIIT/MICT program did not increase EEDE to a greater extent than those completing a 24-week MICT program. No changes were found in RMR. Despite no specific focus on body weight, the combined HIIT/MICT group and the MICT group were associated with significant weight losses of 5 kg and 2 kg, respectively.

If verified by others, our results imply that people with severe obesity should be advised that both combined HIIT/MICT and MICT increase energy expenditure and induce a moderate weight loss, but that HIIT/MICT is associated with a significantly larger weight loss. From a practical point of view, taking into account the high rates of withdrawal and noncompleters in the HIIT/MICT group, it might be appropriate to tailor the treatment to specific patients by informing them of the pros and cons of HIIT/MICT versus MICT.O

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Author contributions: JB conceived and designed the study; analyzed, interpreted, and collected the patient data; and was a major contributor to the writing of the manuscript. JH designed the study, analyzed and interpreted the patient data, and was a major contributor to the writing of the manuscript. JKH designed the study, interpreted the patient data, and contributed to the writing of the manuscript. EG designed the study, collected the patient data, and contributed to writing the manuscript. MCS analyzed and interpreted the patient data and contributed to writing the manuscript. LKJ collected, analyzed, and interpreted the patient data and contributed to writing the manuscript. CM analyzed and interpreted the patient data and contributed to writing the manuscript. EA analyzed and interpreted the patient data and contributed to writing the manuscript. JH interpreted the patient data and contributed to writing the manuscript. ØS designed the study, analyzed and interpreted the patient data, and was a major contributor to the writing of the manuscript. All authors read and approved the final manuscript.

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Data availability: The protocol and data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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