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.

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 function and physical inactivity are common among patients with severe obesity, and severe obesity often have reduced cardiorespiratory fitness (1) and therefore relatively lower energy expenditure during exercise (EEDE). Furthermore, severe obesity often have reduced cardiorespiratory fitness (1) and therefore relatively lower energy expenditure during exercise (EEDE).
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 (VO2max), as VO2max 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 VO2max 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 VO2max. 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.
Results

The primary outcome was the 24-week change in EEDE, and the prespecified secondary outcomes were 24-week changes in RMR, VO2max, 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 VO2max 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 VO2max were performed at the same day to keep the number of test days as low as possible. EEDE, RMR, and VO2max were measured by use of Metalyser, Cortex (2) (Biophysik, Leipzig, Germany). The system was equipped with a mixing chamber with oxygen (O2) and carbon dioxide (CO2), and the ventilation was analyzed continuously. Volume of oxygen consumed (VO2) 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% O2 and 0.03% CO2 and a certified gas containing 15.80% O2 and 4.98% CO2. 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.

VO2max. VO2max (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 VO2max 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 HRmax, Borg scale ≥ 17, and a flattening of the VO2 curve (< 1 mL/min) were used to evaluate whether VO2max had been achieved. VO2max was calculated as the highest of three consecutive 10-second measurements (total 30 s). HRmax 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 VO2max test) on the same treadmill, at 70% of VO2max. The velocity or inclination was adjusted to reach the target intensity based on the VO2max 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% VO2max. 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 VO2/validiation of CO2 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):

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

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

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 VO2max 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 VO2max 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 VO2max, 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 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 VO2max 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). VO2max 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/m2, −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
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
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 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 account that FFM is a key determinant of RMR, and that FFM did not change significantly from week −1 to week 23 in either group (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).

Table 1: Baseline characteristics

|                          | MICT group | HIIT/MICT group |
|--------------------------|------------|-----------------|
| **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%)       |
| **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** |         |                 |
| **VO₂max (L * min⁻¹)**  | 3.20 (0.70) | 3.10 (0.70) |
| **VO₂max (mL * kg⁻¹ * min⁻¹)** | 25.1 (4.1) | 25.9 (4.8) |
| **Energy balance**       |            |                 |
| **Daily activity (CPM)⁵**| 1,707 (467)| 1,609 (580)     |
| **Daily total energy intake (kcal * d⁻¹)⁶** | 2,890 (877) | 2,383 (969) |

Data presented as numbers (%) or mean (SD).
CPM, counts per minute; VO₂max, maximum volume of oxygen consumed.

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 VO₂max

EEDE and VO₂max 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 VO₂max, as VO₂max defines the potential for EEDE (8). Furthermore, our finding that 8 weeks of HIIT (week 8 to week 16) increased VO₂max and EEDE 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 VO₂max.

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).
| Primary outcome | MICT group | HIIT/MICT group | Between-group differences (95% CI) | P value between group |
|-----------------|------------|----------------|------------------------------------|----------------------|
| Energy expenditure during exercise | 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 | Baseline | 52.0 (26.6 to 77.3) | 66.7 (18.7 to 118) | −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) | 43.1 (21.1 to 65.0) | −36.5 (6.4 to 66.5) | 0.019 |
| | Percent change | 0.9 | 6.6 | - | - |
| Resting metabolic rate (kcal * d⁻¹) | 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 2,621) | 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 2679) | 127 (−189 to 442) | 0.421 |
| Change from baseline to 24 weeks | Baseline | 31.3 (−44.3 to 107) | 38.1 (−102 to 182) | −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) | −84.5 (−160 to −8.9) | 20.4 (−173 to 133) | 0.788 |
| | Percent change | 2.5 | 3.5 | - | - |
| Cardiorespiratory fitness | 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) | 3.29 (2.95 to 3.65) | 0.16 (−0.29 to 0.61) | 0.481 |
| | 16 weeks | 3.46 (3.16 to 3.76) | 3.37 (2.98 to 3.76) | 0.25 (−0.19 to 0.70) | 0.255 |
| | 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 | Baseline | 0.30 (0.22 to 0.38 | 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) | 0.13 (0.05 to 0.24) | −0.14 (0.02 to 0.25) | 0.023 |
| | Percent change | 0.3 | 4.1 | - | - |
| BMI (kg * m⁻²) | 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)
|                          | MICT group     | P value within group | HIIT/MICT group | P value 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 (7.1 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 (9.4 to 20.2) | 0.042 |
| 8 weeks                  | 72.7 (65.8 to 79.7) | −                    | 62.3 (56.5 to 68.2) | −                | 10.4 (9.9 to 19.9) | 0.033 |
| 16 weeks                 | 73.5 (66.6 to 80.4) | −                    | 60.3 (53.0 to 67.7) | −                | 13.2 (8.2 to 23.2) | 0.111 |
| 24 weeks                 | 73.1 (66.1 to 80.2) | −                    | 62.0 (55.8 to 68.3) | −                | 11.2 (5.1 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)
|                          | 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.
Because the study aimed to investigate the potentially different effects of exercise programs of varying intensity on physiological measures, the measured effects immediately after each of the three 8-week periods should be considered exploratory. However, 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). 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$_{2\text{max}}$ 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 advisable to tailor the treatment to specific patients by informing them of the pros and cons of HIIT/MICT versus MICT.
Acknowledgments
This study was organized by the Morbid Obesity Centre, Vestfold Hospital Trust. We thank all the patients who took part in this study, the study personnel, and employees; we also thank Linda Mathiesen, Inger Marie Flakstad, Randi Storåld Lund, Hildegunn Baarnes, Stine Merete Larsen, Berit Moshing Bjørkås, Andreas Horsdal (Clinic Medicine and Rehabilitation), Mona Sæbø (University of South-Eastern Norway), Tor-Ivar Karlsen (University of Agder), and the master students (University of South-Eastern Norway) for sampling and logistics assistance. Thanks are also due to Matthew McGee for proofreading the manuscript.

Funding agencies: This study was funded by the Vestfold Hospital Trust (Morbid Obesity Centre and the Clinic of Medicine and Rehabilitation) and the University of South-Eastern Norway. All employees receive a salary from their respective departments.

Disclosure: The authors declared no conflict of interest.

Author contributions: JS 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, collected the patient data, and contributed to writing the manuscript. MK designed the study, collected the patient data, and contributed to writing the manuscript. EG designed the study, collected the patient data, and contributed to writing the manuscript. MJS analyzed and interpreted the patient data and contributed to writing the manuscript. UJTJ 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. JKH 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.

Clinical trial registration: ClinicalTrials.gov identifier NCT02311736 (December 8, 2014) and Regional Committees for Medical and Health Research Ethics (REC) South East Norway identifier 2013/1848 (October 23, 2013).

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.

References
1. Berge J, Storen O, Hertel JK, Gjevestad E, Smausten MC, Hjelmesea J. Associations between cardiorespiratory fitness and weight loss in patients with severe obesity undergoing an intensive lifestyle intervention program: retrospective cohort study. BMC Endocr Disord 2019;19:6; doi:10.1186/s12902-019-0394-z
2. de Souza SA, Fairclough J, Sant’ana AF. Effect of weight loss on aerobic capacity in patients with severe obesity before and after bariatric surgery. Obes Surg 2010;20:871-875.
3. Brien SE, Katzmarzyk PT, Craig CL, Gauvin L. Physical activity, cardiorespiratory fitness and body mass index as predictors of substantial weight gain and obesity: the Canadian physical activity longitudinal study. Can J Public Health 2007;98:121-124.
4. Kantaritzis K, Thamer C, Peter A, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. Gut 2009;58:1281-1288.
5. Dyrsad SM, Edvardsen E, Hansen BH, Andersen SA. Waist circumference thresholds and cardiorespiratory fitness. J Sport Health Sci 2019;8:17-22.
6. Miller WM, Spring TJ, Zalesin KC, et al. Lower than predicted resting metabolic rate is associated with severely impaired cardiorespiratory fitness in obese individuals. Obesity (Silver Spring) 2012;20:405-511.
7. Ando T, Piaggi P, Bogardus C, Krakoff J. VO2max is associated with measures of energy expenditure in sedentary condition but does not predict weight change. Int J Sports Med 2005;26:537-541.
8. Turley K, Stanforth P, Rankinen T, et al. Scaling submaximal exercise cardiac output and stroke volume: the HERITAGE Family Study. Int J Sports Med 2006;27:205-211.
9. Johansen JM, Eriksen S, Sunde A, Slettemoeb ØB, Helgerud J, Støren Ø. Improving utilization of maximal oxygen uptake and work economy in recreational cross-country skiers with high-intensity double-poling intervals. Int J Sports Physiol Perform 2019;14:255-262.
10. Storen O, Helgerud J, Sæboe M, et al. The effect of age on the VO2max response to high-intensity interval training. Med Sci Sports Exerc 2017;49:78-85.
11. Fullmer S, Benson-Davies S, Earthman CP, et al. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. J Acad Nutr Diet 2015;115:1417-1446.e2.
12. Mc Ardle WDK, Frank I, Katch VL. Exercise Physiology: Nutrition, Energy, and Human Performance, 7th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.
13. Samaras TT. Human Body Size and the Laws of Scaling: Physiological, Performance, Growth, Longevity and Ecological Ramifications. Nova Science; 2007.
14. Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr 1989;49:968-975.
15. Wolf-Hughes DL, Bassett DR, Fitzhugh EC. Population-referenced percentiles for waist-worn accelerometer-derived total activity counts in U.S. youth: 2003-2006 NHANES. PLoS One 2014;9:e115915. doi:10.1371/journal.pone.0115915
16. Andersen LF, Solvoll K, Johannsen LR, Aaro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999;150:75-87.
17. Johansson LSK, Bjorneboe GE, Drevon CA. Dietary habits among Norwegian men and women. Scand J Nutr 1997;99:67-70.
18. Norwegian Food Composition Database. Norwegian Food Safety Authority. 2018. https://www.matportalen.no/2017. Accessed May 25, 2018.
19. Martins C, Truby H, Morgan LM. Short-term appetite control in response to a 6-week exercise programme in sedentary volunteers. Br J Nutr 2007;98:834-842.
20. Rogromo Ø, Helteland E, Helgerud J, Hoff J, Slordahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil 2004;11:216-222.
21. Brouns TL, Ho YY, Rollo ME, Collins CE. Validity of dietary assessment methods when compared to the method of doubly labeled water: a systematic review in adults. Front Endocrinol (Lausanne) 2019;10:850. doi:10.3389/fendo.2019.00850
22. Stiegler P, Cumlielle A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med 2006;36:239-252.
23. MacKenzie-Shalders K, Kelly JT, So D, Coffey VG, Byrne NM. The effect of exercise interventions on resting metabolic rate: a systematic review and meta-analysis. J Sports Sci 2020;38:1635-1649.
24. Speckman JR, Selman C. Physical activity and resting metabolic rate. Proc Nutr Soc 2003;62:621-634.
25. Gore CJ, Withers RT. The effect of exercise intensity and duration on the oxygen deficit and excess post-exercise oxygen consumption. Eur J Appl Physiol Occup Physiol 1990;60:169-174.
26. Larsen I, Welde B, Martins C, Tjonna AE. High- and moderate-intensity aerobic exercise and excess post-exercise oxygen consumption in men with metabolic syndrome. Scand J Med Sci Sports 2014;24:e174-e179.
27. Bahr R, Sejersted OM. Effect of intensity of exercise on excess postexercise O2 consumption. Metabolism 1991;40:836-841.
28. Sharp TA, Reed GW, Sun M, Abumrad NN, Hill JO. Relationship between aerobic fitness level and daily energy expenditure in weight-stable humans. Am J Physiol 1992;263:E205-211.
29. Catenacci VA, Wyatt HR. The role of physical activity in producing and maintaining weight loss. Nat Clin Pract Endocrinol Metab 2007;3:518-529.
30. Fisher G, Brown AW, Bohan Brown MM, et al. High intensity interval- vs moderate-intensity training for improving cardiometabolic health in overweight or obese males: a randomized controlled trial. PLoS One 2015;10:e0138853. doi:10.1371/journal.pone.0138853
31. Pedersen LR, Olsen RH, Ahlomn C, et al. Effects of 1 year of exercise training versus combined exercise training and weight loss on body composition, low-grade inflammation and lipids in overweight patients with coronary artery disease: a randomized trial. Cardiovasc Diabetol 2019;18:127. doi:10.1186/s12933-019-0934-x