

BMJ Open Isolated and combined effects of high-intensity interval training and time-restricted eating on glycaemic control in reproductive-aged women with overweight or obesity: study protocol for a four-armed randomised controlled trial

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ABSTRACT

Introduction Overweight and obesity in reproductive-aged women is a global problem due to the increased risk of subfertility, pregnancy complications and cardiometabolic diseases. High-intensity interval training and time-restricted eating are two primary lifestyle interventions that, independently, have positive effects on a range of health outcomes. Whether these two strategies have synergistic effects is currently unknown. Our primary aim is to determine the isolated and combined effect of high-intensity interval training and time-restricted eating on glycaemic control in reproductive-aged women with overweight/obesity.

Methods and analysis The study is a randomised controlled trial with four parallel groups. Women (N=120) aged 18–45 years with body mass index ≥ 27 kg/m² will be randomly allocated (1:1:1:1) to either: (1) high-intensity interval training, (2) time-restricted eating, (3) a combination of high-intensity interval training and of time-restricted eating, or (4) a control group. The duration of each intervention will be 7 weeks. The primary outcome measure will be glycaemic control, determined by the total area under the plasma glucose curve over 2 hours after a 75-gram oral glucose tolerance test. Secondary outcome measurements will include markers of cardiovascular and metabolic health (peak oxygen uptake, blood pressure, blood lipids, body composition, insulin sensitivity), sleep quality, physical activity, diet and adherence rates to the intervention.

Ethics and dissemination The Regional Committee Medical Research Ethics, Norway has approved the trial protocol. This study will provide important new knowledge to both the scientific community and the general population about the isolated and combined effects of two novel diet–exercise strategies on cardiovascular and metabolic health among women with overweight/obesity.

Trial registration number NCT04019860.

Strengths and limitations of this study

- This will be the first randomised controlled trial to determine if time-restricted eating confers additive cardiometabolic health benefits above and beyond those induced by high-intensity interval training.
- We will include women with overweight/obesity of reproductive age to assess if time-restricted eating and high-intensity interval training are feasible strategies to rapidly improve glycaemic health in this population.
- Due to the difficulty blinding investigators and participants to behavioural interventions, investigators will not be blinded for outcome assessments.
- Due to the COVID-19 outbreak, it is likely we will lack outcome assessments from some participants, and physical activity and dietary habits may change during the intervention period for some participants.

INTRODUCTION

The prevalence of obesity is increasing in almost every country, with approximately 40% of the adult population now considered overweight or obese.¹ There is an accelerated increase in obesity prevalence among young adults,² which is of particular concern for women due to the associated risks of subfertility and pregnancy complications.^{3 4} Furthermore, obesity and insulin resistance in women of reproductive age not only increases the women's own risk for future cardiometabolic disease,^{5 6} but also predisposes her offspring for adverse health outcomes.^{7–9} Lifestyle changes, including increased physical activity and a healthy diet, are recommended as first-line treatment of obesity, but many individuals fail to adhere



to such advice because of a lack of time or motivation. About two-thirds of Norwegian adults fail to adhere to the current recommendations to accumulate at least 150 min/week of moderate-intensity physical activity, and individuals with obesity are 63% less likely to adhere to these recommendations than normal-weight individuals.¹⁰ Moreover, a large proportion of adults fail to comply with the Nordic Nutrition Recommendations in regards to intake of fibre and have higher than the maximum recommended intake of saturated fat.¹¹ As more socially acceptable and achievable diet–exercise strategies, high-intensity interval training (HIIT) and time-restricted eating (TRE) hold promise as alternatives to current recommendations to improve metabolic health among reproductive-aged women.¹²

HIIT, defined as short periods of intense activity separated by low-intensity breaks, leads to greater improvements in insulin sensitivity, cardiorespiratory fitness and body composition than those induced by continuous moderate-intensity training in subjects at increased risk for cardiometabolic diseases.^{13–15} Even short-term (6 weeks) HIIT, with brief (15–60 s) work-bouts and a total time commitment of <45 min/week, improves insulin sensitivity and glycaemic control to a similar magnitude as that attained after 6 months of traditional high-volume endurance training.^{16 17} HIIT is feasible and enjoyable among women with obesity¹⁸ and is enjoyed more than traditional endurance training.¹⁹ Because HIIT is also a time-efficient intervention, it has the potential to increase adherence and participation rates in physical activity at both the individual and population level. Indeed, the adherence to three weekly HIIT sessions among women with overweight/obesity was 85%–90%, with ~20% improvements in insulin sensitivity after just 10 weeks.^{20 21} Improvements in body composition are also greater after HIIT compared with traditional endurance training in individuals with obesity,¹⁵ making HIIT a potent intervention that elicits important changes in a range of clinically relevant health outcomes in reproductive-aged women.

TRE is a novel eating regimen in which the duration of fasting between the last evening meal and the first meal of the next day is prolonged. Reducing the time window for energy intake from 12 to 14 to ≤8–10 hours/day reduces obesity, inflammation and insulin resistance in both rodent models²² and humans,^{23–28} independent of any deliberate change in total energy intake and/or food composition. TRE had been demonstrated to be a feasible and practical approach to improve cardiometabolic health in men with overweight/obesity²⁷ and individuals with type 2 diabetes.²⁹

Although dietary interventions and exercise training can, independently, improve cardiometabolic health, the overall effects of combining diet and exercise are usually superior to each strategy's isolated effects.³⁰ TRE and HIIT independently improve glycaemic control^{24 31} but whether combining these two strategies can induce a synergistic improvement in insulin sensitivity is currently unknown.³²

Aims

Effective and feasible diet–exercise strategies that can improve metabolic health in reproductive-aged women are needed to reduce the risks for adverse pregnancy outcomes. Therefore, the primary aim of this trial is to determine the isolated and combined effects of 7 weeks of HIIT and TRE on glycaemic control among women with overweight/obesity. We hypothesise that:

1. Both HIIT and TRE will improve glycaemic control.
2. The combination of both interventions will induce larger improvements in glycaemic control than each individual strategy alone.

Secondary aims are to determine if HIIT and TRE, and the combination of these interventions, will induce improvements in insulin sensitivity, body composition, cardiorespiratory fitness, blood pressure, circulating markers of cardiovascular and metabolic health, and sleep. We will also record the adherence to TRE and HIIT, ratings of appetite and hunger, physical activity, and dietary intake.

METHODS

Study setting and recruitment

This is a single-centre, randomised controlled trial with four parallel groups; three intervention groups and one control group. Data collection will be completed at the Norwegian University of Science and Technology (NTNU) in Trondheim, Norway. The testing and training of participants will take place in the NeXt Move Core Facility and research laboratories at the Faculty of Medicine and Health Sciences, NTNU. Participants will be recruited from public announcement at the university homepages and through advertisements in social media. Written informed consent will be obtained from all participants prior to participation.

Participants

To be eligible for participation, women will have to meet the following criteria:

- ▶ Aged 18–45 years old.
- ▶ Body mass index ≥ 27.0 kg/m².
- ▶ Able to walk on a treadmill or ride a bike at least 60 min (self-reported).
- ▶ Be able to attend laboratory assessments and training sessions at NTNU.

Women will not be eligible for participation if they meet any of the following criteria:

- ▶ Pregnant.
- ▶ Breast feeding within 24 weeks of study commencement.
- ▶ Known cardiovascular disease, type 1 or type 2 diabetes.
- ▶ Currently taking antihypertension medication.
- ▶ Currently taking glucose-lowering or lipid-lowering medication.
- ▶ Habitual eating window <12 hours/day.

CONSORT 2010 Flow Diagram

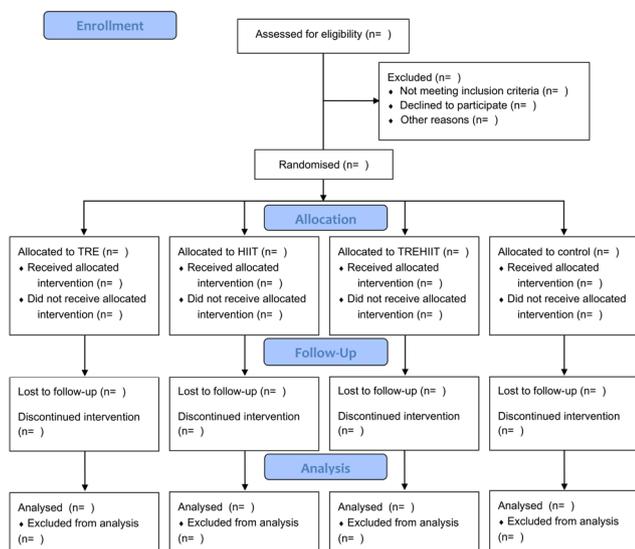


Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; HIIT, high-intensity interval training; TRE, time-restricted eating; TREHIIT, TRE and HIIT.

- ▶ Habitually performing HIIT more than once per week.
- ▶ Body mass variation >4 kg 3 months prior to study commencement.
- ▶ Shift work that includes night shifts.

Randomisation and allocation

Participants will be allocated 1:1:1:1 to TRE, HIIT, TRE and HIIT (TREHIIT), or control after baseline assessments (figure 1). We will use a computer random number generator developed and administered at the Faculty of Medicine, Department of Public Health and General Practice, NTNU, Trondheim, Norway to allocate participants. The randomisation will have varying block sizes, with the first, the smallest and the largest block defined by the computer technician at the Unit for Applied Clinical Research at NTNU. The investigator enrolling the participants (TM) will be informed about the allocation results on screen and by email after registration of each new participant and will not have the full randomisation list available.

Interventions

The TRE and HIIT protocols will be identical for participants allocated to TREHIIT as for participants allocated to only one of the interventions.

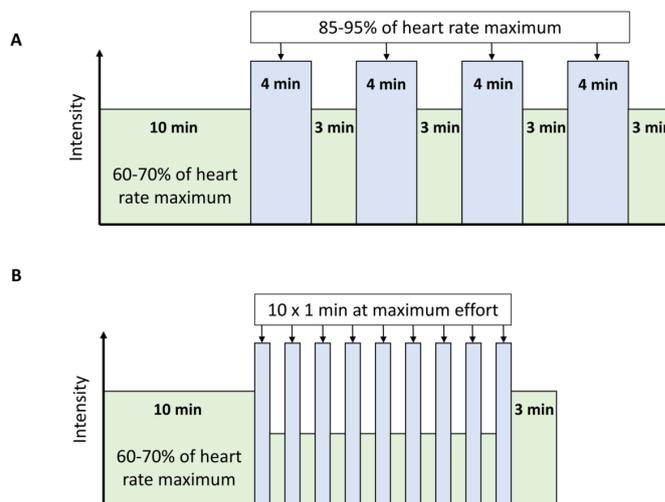


Figure 2 High-intensity interval training (HIIT) protocol. (A) Two weekly sessions will be 4×4 min HIIT; four 4 min work-bouts at 85%–95% of heart rate maximum, separated by 3 min recovery at 60%–70% of heart rate maximum. (B) One weekly session will be 10×1 min HIIT; 10 1 min work-bouts at the maximum intensity the participants can sustain, separated by 1 min low-intensity activity.

Time-restricted eating

Participants will be asked to reduce their daily time window for energy intake to a maximum of 10 hours/day. They can choose when to begin their eating window but will be advised that the last meal should be completed before or at 2000 hours. We will give participants no advice on what to eat/drink, nor about the total energy intake. During the fasting period, participants will be allowed to consume non-energy-containing beverages. We will provide motivational support to enhance adherence through weekly phone calls/short message service/email, and/or face-to-face (for the participants who will also be undertaking HIIT).

High-intensity interval training

Participants will exercise three times per week in the laboratory, according to the protocol used in a previous study.²⁰ Two of the sessions will be 4×4 min HIIT and one session will be 10×1 min HIIT (figure 2). Participants will walk or run on a treadmill. If required (due to physical limitations, for example, knee pain), they can choose to exercise on a stationary bike instead. The exercise sessions will be supervised, and exercise intensity will be recorded at every session, using heart rate monitors (Polar, Finland). We will adjust the absolute workload of the HIIT sessions throughout the intervention period to account for changes in cardiorespiratory fitness. The scheduled total weekly exercise time will be 109 min.

Control group

Participants in the control group will be asked to continue with their habitual physical activity and dietary habits. We will contact the participants in the control group once per week to support adherence to registrations and monitoring. After the completion of the intervention

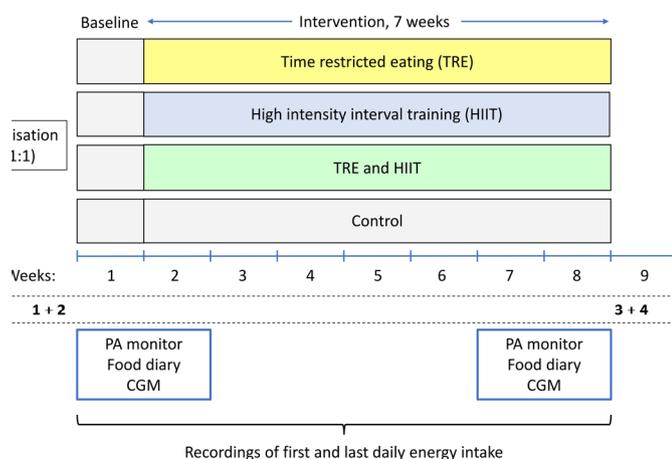


Figure 3 Experimental design. CGM, continuous glucose monitor; HIIT, high-intensity interval training; PA, physical activity; TRE, time-restricted eating.

period and post-intervention assessments, participants in this group will be offered a ‘delayed treatment’ option whereby they can choose to undertake one of the study interventions with full support and supervision for 7 weeks.

Experimental protocol and outcome measures

The study period will be 8–9 weeks, with the 7-week intervention commencing after 1 week of baseline measurements during which all participants will continue with their habitual dietary intake and physical activity patterns (figure 3). Participants will come in for assessments in the laboratory on 2 separate days at baseline and on 2 separate days after the intervention period. These assessments will be undertaken in the follicular phase of the menstruation cycle in participants with a regular cycle. We will instruct participants to abstain from vigorous physical activity for ≥ 48 hours prior to the measurements. If not otherwise specified, outcome measures will be assessed at baseline and after the intervention period.

Primary outcome measure and secondary glycaemic control measures

The primary outcome measure will be glycaemic control, measured as the total area under the plasma glucose curve (tAUC) over 2 hours after a 75 g oral glucose tolerance test (OGTT). The tAUC will be integrated using the trapezoid rule.³³ We will also calculate tAUC for insulin and the incremental area under the curve (using fasting concentrations as baseline values) for circulating glucose and insulin concentrations using the trapezoid method, and peak concentrations during the OGTT. After an overnight fast (≥ 10 hours), the participants will consume 75 g of glucose diluted in 250 mL water. Blood will be sampled for insulin and glucose concentrations at 0 (prior to the OGTT), 30, 60, 90 and 120 min from an indwelling catheter. Additionally, we will measure glycated haemoglobin (HbA1c). We will estimate insulin sensitivity using the

homeostasis model assessment-estimated insulin resistance; fasting serum insulin in $\mu\text{U/mL} \times \text{fasting plasma glucose in mmol/L} / 22.5$.³⁴ Participants will wear continuous glucose monitors (CGMs, FreeStyle Libre 2, Abbott Diabetes Care, Norway) for 14 days commencing at the beginning of the study (the baseline week and the first week of the intervention) and 14 days at the end of the study (the last 2 weeks of the intervention, figure 3). From these measurements, we will determine 24-hour glycaemic control, 3-hour postprandial glucose levels (AUC) for the first meal of the day and nocturnal glycaemic control. The CGMs will be ‘masked’ for the participants, so they will not be able to see their glucose levels.

Body composition

Total body mass and body composition will be estimated in the morning after an overnight fast with the participants wearing light clothing and without shoes or socks using bioelectrical impedance analysis (InBody720, Biospace CO, Korea). We will measure height with the participants standing, without shoes, using a standard stadiometer.

Blood sampling and biochemistry

In addition to glucose concentration and HbA1c, analysis of fasting venous blood samples will include measurements of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides concentrations. Blood sample collection will be performed in accordance with laboratory standard procedures. Immediately after sampling, serum glucose, HbA1c and blood lipids will be analysed at the St Olavs Hospital, according to their standard procedures. Additional blood samples (serum, full blood and EDTA plasma) will be immediately frozen at -80°C and stored in a biobank for later analyses. These later analyses will include, but are not limited to, insulin concentrations.

Cardiorespiratory fitness and maximum heart rate

Peak oxygen uptake (VO_2peak) will be measured using indirect calorimetry (MetaMax II Portable CPX System, Cortex, Germany). Participants will walk or run on a treadmill until volitional exhaustion. We will use an individualised protocol in which the test starts after a 10-minute warm-up and the speed or inclination will be increased every 1–2 min, by 0.5–1.0 km/hour or 1%–2%. VO_2peak will be determined as the highest consecutive 30 s measured and reported as both absolute (L/min) and relative (mL/min/kg) values. Criteria for attainment of VO_2peak will be a levelling off in O_2 uptake, a respiratory exchange ratio >1.10 and/or volitional exhaustion.³⁵ We will record heart rate during the exercise tests and use the peak heart rate recorded during the test as an estimate of heart rate maximum.³⁶

Blood pressure and resting heart rate

We will use an automatic blood pressure device (Philips IntelliVue MP50, Philips Medizin Systeme, Germany) to measure blood pressure and resting heart rate after the participants have rested in a seated position for 15 min.

We will report the average of three measurements taken 1 min apart.

Physical activity, sleep and diet

Physical activity levels, energy expenditure and sleep duration will be estimated using activity monitors (Sensewear Armbands, BodyMedia, Pennsylvania, USA) during the same two 14-day periods as participants wear CGMs (figure 3). Participants will complete questionnaires regarding their physical activity levels (International Physical Activity Questionnaire), sleep quality (Pittsburgh Sleep Quality Index) and chronotype (Hornestberg Morningness Eveningness Questionnaire). We will report self-reported data on physical activity in both categories (low, moderate and high activity levels) and as a continuous variable (metabolic equivalent task minutes per week). Participants will complete an electronic food diary (www.kostholdsplanleggeren.no) during the 14-day periods at the beginning and the end of the trial (figure 3). From the diet diaries, we will determine total energy intake, macronutrients and core food group intake. During the same periods, participants will rate their hunger and satiety in the morning (before breakfast) and evening (just before going to bed) using visual analogue scales. They will also report the time for their first and last energy intake every day throughout the study period in a diary.

Adherence to interventions

Adherence to TRE will be recorded as the average daily time window for energy intake and the number of days per week that participants adhere to a ≤ 10 -hour time window for energy intake. For HIIT, adherence will be recorded as the number of HIIT sessions the participants complete divided by the number of scheduled sessions, as well as the percentage of HR maximum during the HIIT sessions. We will also report rates of perceived exertion during HIIT sessions, according to the Borg 6–20 scale.³⁷

Adverse effects

We will document and report adverse events during training and testing, as well as any adverse events relating to TRE.

Changes in the protocol due to the COVID-19 outbreak

Before the COVID-19 outbreak and the enforcement of laboratory restrictions on 12 March 2020, we had completed all assessments from 40 participants. Participants who were randomised and baseline tested when the laboratories closed in March 2020 will be included in the intention-to-treat analysis; we will include and report all the data we have on these participants. Six participants were randomised but had not yet started the intervention at the time of lab closure. These participants were invited to complete new baseline assessments and continue in the group they were allocated to when the lab reopened in August 2020, if they still met the inclusion criteria. For those participants who had already commenced exercise training at the time of lab closure, we offered to continue supervised training as outdoor uphill walking/running

or to complete the sessions unsupervised. The same recordings of number of sessions completed and the relative exercise intensity applied to these participants. We were able to post-test some of the participants who were included during this period (n=13).

Sample size and statistical analysis

Sample size

We calculated sample size based on a previous 6-week study on HIIT in overweight reproductive-aged women, where they reported an improvement of -54 (SD 64 mmol/L) in glucose tAUC.³¹ To detect such a difference between the HIIT group and the control group, with a statistical power of 80% and an alpha level of 0.05 (two-sided), a minimum of 24 participants in each group was required. The power calculation is based on an independent t-test (two-sided) between these two groups, as there are insufficient data to guide a power calculation for the comparison between all four groups (ie, no data on the effects of TRE and/or the combination of TRE and HIIT in this population). However, in our analyses we will compare all four groups. We aim to include 120 participants in this study, 30 in each group, allowing for an expected dropout rate of 15%, and will consider including more participants in the trial when we know how many dropout/incompletions are likely because of the COVID-19 restrictions.

Statistical analyses

Our primary analyses will include all the data we obtain, irrespective of adherence to the interventions (intention-to-treat). We will perform a secondary analysis where we include those participants who have adhered to the protocols and who report that the COVID-19 situation has not affected their normal dietary intake and levels of physical activity. In this per-protocol analysis, participants assigned to TRE will be included if they report a daily window for energy intake ≤ 10 hours on 5 or more days throughout the intervention period, whereas women assigned to HIIT will be included if they have completed ≥ 16 training sessions at an intensity of $\geq 85\%$ of HR maximum. We will use linear mixed models to test differences between groups. In these models, we will adjust for the baseline values of the outcome as a covariate, as recommended by Twisk *et al.*³⁸ P values of < 0.05 will be considered significant for both the primary and secondary outcome measures. However, due to multiple hypotheses, p values of 0.01–0.05 will be interpreted with caution.

Blinding

We are unable to blind group allocation to participants or study personnel due to the nature of the intervention, but baseline assessments will be undertaken prior to randomisation. We will perform all the statistical analyses blinded for group allocation.

Patient and public involvement

No patients were involved in the development of the research question or design of the study. Individual results



will be disseminated to each participant. We will also send out a summary of the study results to all participants at completion of the study.

Ethics and dissemination

The study is approved by the Regional Committee Medical Research Ethics in North Norway (approval number 11496), has its origin in the Declaration of Helsinki and is consistent with ICH/Good Clinical Practice and applicable regulatory requirements. All protocol modification will be reported to the Regional Committee Medical Research Ethics. Data will be entered into an electronic case report form, using only ID numbers as identifiers for the participants. We will ensure data quality by double data entry. We will publish the results from the study as peer-reviewed articles in international journals and communicate the results at national and international conferences and through social media.

DISCUSSION

To the best of our knowledge, this will be the first study to determine the combined effects of HIIT and TRE on cardiometabolic health. Our hypothesis is that the combination of these two interventions will induce synergistic and clinically relevant improvements for a range of health outcomes in women with overweight/obesity. We believe that it will be feasible for the participants in our study to adhere to both HIIT and TRE for 7 weeks and that such interventions could offer viable alternatives to current exercise–nutrition recommendations for this population.

There are only two previous studies on the combination of TRE and exercise training in humans.^{39 40} Both these investigations determined whether TRE could have an additive effect to resistance training on body composition in healthy men. Moro *et al*³⁹ reported that participants who undertook TRE in addition to resistance training decreased total body mass and fat mass, compared with the participants randomised to a resistance training only intervention. In contrast, Tinsley *et al*⁴⁰ reported no additional effect of TRE undertaken in combination with a resistance training programme on body composition. In both these studies the researchers compared exercise training only with exercise training and TRE, and no prior studies have investigated the potential for an additive benefit of exercise training to a TRE dietary regimen compared with TRE alone.

Because of the COVID-19 outbreak in early 2020, the data collection and HIIT intervention in this study had to be ceased and/or modified. This will have consequences for the number of dropouts, missing data and proposed timeline of the study. Some of the participants who were included but had not yet completed the intervention when new restrictions about working from home and shutdown of laboratory/gyms were enforced will likely change their physical activity and dietary habits because of their new environmental situation. Accordingly, we may need to include more participants than originally

proposed and will undertake both intention-to-treat and per-protocol analyses.

We chose to include an option of delayed treatment for participants initially allocated to the control group as such a policy is a motivational factor for those initially allocated to the control group, enhancing the likelihood for them to return in for assessments after the intervention period. This delayed treatment period will also reduce the probability of participants in the control group commencing exercise training and/or changing dietary habits during the intervention period (ie, contamination).

There is an urgent need for effective, practical and feasible diet–exercise strategies to improve the metabolic health for reproductive-aged women with overweight/obesity. If the interventions employed in the current study are shown to be feasible and effective, they are practical to implement among all adults with overweight/obesity, and in particular among women who are planning a pregnancy and who wish to optimise their metabolic health before conception.

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Contributors TM drafted the manuscript. TM, JAH, CPS and SL conceived and contributed to the design of the study and to the plan for analyses. TM and CPS will coordinate the study, perform measurements on test days, monitor participants and supervise the exercise training. All authors provided feedback and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

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