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# 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:** Women in reproductive age should improve their metabolic health to reduce the risk for pregnancy complications and the susceptibility to future cardiometabolic diseases in their offspring. High intensity interval training and time-restricted eating are two diet-exercise interventions showing promising effects on a range of health outcomes, but 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=116) aged 18-45 with body mass index (BMI) $\geq$ 27 kg/m$^2$ will be randomly allocated (1:1:1:1) to; high-intensity interval training, time-restricted eating, the combination of high intensity interval training and of time-restricted eating, or a control group. The intervention period will be 7 weeks. The primary outcome measure is glycaemic control, measured as the total area under the plasma glucose curve over two hours after a 75-gram oral glucose tolerance test. Secondary outcome measurements include markers of cardiovascular and metabolic health, as well as adherence rates.

**Ethics and dissemination:** The Regional Committee Medical Research Ethics, Norway, has approved the trial protocol. This study will provide important 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.

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**Trial registration number:** Clinical trial gov NCT04019860.

**Keywords:** exercise, physical activity, diet, insulin sensitivity, body composition

**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 in 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.
- We will lack outcome assessments from some participants and physical activity and dietary habits may change during the intervention period for some participants due to the COVID-19 outbreak.

## INTRODUCTION

Obesity and insulin resistance in women of reproductive age not only increases the women's own risk for future cardiometabolic disease[1 2], but also predisposes her baby for adverse health outcomes.[3-5] 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 these advices because of a lack of time or motivation. More socially acceptable and achievable diet-exercise strategies, such as high intensity interval training (HIT) and time-restricted eating (TRE), hold promise as alternative strategies to improve metabolic health among reproductive-aged women.[6]

HIT, 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.[7-9] Even short-term (6 weeks) HIT with brief (15-60 sec) work-bouts and a total time commitment of < 45 min per week, improves insulin sensitivity and glycaemic control similar to that attained after 6 months of traditional high-volume endurance training.[10 11] HIT has proven to be feasible and enjoyable among women with obesity.[12] Due to the greater enjoyment of HIT compared to traditional endurance training[13], as well as the time-efficiency, such exercise strategies have a better potential for adherence. Indeed, the adherence to three

weekly HIT sessions was 85-90% among women with overweight/obesity, and insulin sensitivity increased by ~20% after 10 weeks.[14 15] Improvements in body composition are also larger after HIT compared to traditional endurance training in individuals with obesity.[9] In summary, HIT is a highly potent intervention that elicits important changes in a range of clinically relevant health outcomes in reproductive-aged women.

TRE is a novel eating regimen whereby the duration of fasting between the last evening meal and the first meal of the next day is prolonged. Usually, the time-window for energy intake is restricted to ≤ 8-10 hours/day. Such an eating pattern reduces obesity, inflammation and insulin resistance in both rodent models[16] and humans[17-21], independent of any deliberate change in total energy intake and/or food composition. TRE can be a feasible approach to improve cardiometabolic health and was perceived as a practical dietary strategy in men with overweight/obesity.[21]

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 independent effects.[22] TRE and HIT independently improve glycaemic control [18 23] but whether combining these two strategies can induce a synergistic improvement in insulin sensitivity is currently unknown.[24]

AIMS

The primary aim of this trial is to determine the isolated and combined effects of HIT and TRE for 7 weeks on glycaemic control among reproductive-aged women with overweight/obesity. We hypothesise that:

1) Both HIT and TRE will improve glycaemic control.
2) The combination of both strategies will induce larger improvements than each individual strategy.

Secondary aims are to determine if HIT and TRE will induce improvements in insulin sensitivity, body composition, cardiorespiratory fitness, blood pressure, circulating markers of cardiovascular and metabolic health, and sleep. Additionally, we will record the adherence to TRE and HIT, 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 NextMove 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. A 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 (BMI) ≥ 27.0 kg/m$^2$
- Able to walk on a treadmill or ride a bike at least 60 min

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

- Pregnant
- Breastfeeding within 24 weeks of study commencement
- Known cardiovascular disease, type 1 or type 2 diabetes
- Currently taking anti-hypertension medication
- Currently taking glucose- or lipid lowering medication
- Habitual eating window < 12 hours/day
- Habitually performing HIT more than once per week
- Body mass variation > 4 kg three months prior to study commencement
- Shift work that includes night shifts

### Randomisation and allocation

Participants will be allocated 1:1:1:1 to TRE, HIT, both TRE and HIT (TREHIT), 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 (T.M.) will be informed about the allocation results on screen and by e-mail after registration of each new participant and will not have the full randomisation list available.

**Interventions**

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

*Time-restricted eating*

Participants will be asked to reduce their daily time-window for energy intake to a maximum of 10 hours. They can select when to start eating in the day but will be advised that the last meal should be completed before or at 20:00. We will give no advice what to eat/drink, nor about the total caloric intake. During the fasting period, they we be allowed to consume non-caloric drinks. We will provide adherence and motivation support through weekly phone calls/SMS/email, and/or face-to-face (for the participants who will also be undertaking HIT).

*High intensity interval training*

Participants will exercise three times per week at the laboratory, according to the protocol used in a previous study.[14] Two of the sessions will be 4 x 4 min HIT and one session will be 10 x 1 min HIT (Figure 2). Participants will walk or run on a treadmill. If required (due to injury or pain), they can 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 HIT sessions throughout the intervention period to account for changes in cardiorespiratory fitness. The scheduled total weekly exercise time will be 109 minutes.

*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 period and post-intervention assessments, they will be offered a "delayed treatment" where they can choose to undertake one of the study interventions. If they wish to do this, we will offer them support and supervision for 7 weeks.

**Experimental protocol and outcome measures**

The study period will be 8-9 weeks, with the 7-week intervention starting after one week of baseline measurements where all participants will continue with their habitual dietary intake and physical activity (Figure 3). Participants will come in for assessments in the laboratory on two separate days at baseline and on two 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 the participants to abstain from vigorous physical activity for ≥ 48 h 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 (AUC) over 2 h after a 75 g oral glucose tolerance test (OGTT). We will also calculate the incremental area under the curve (iAUC; using fasting concentrations as baseline values) using the trapezoid method, for circulating glucose and insulin concentrations, and peak concentrations during the OGTT. After an overnight fast (≥ 10 h), the participants will consume 75 g of glucose diluted in 250 mL water. Blood will be sampled for insulin and glucose measurements at 0 (prior to the OGGT), 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 (HOMA-IR); fasting serum insulin in µU/mL x fasting plasma glucose in mmol/L/22.5.[25] Participants will wear continuous glucose monitors (CGMs, FreeStyle Libre 2, Abbott Diabetes Care, Norway) for 14 days in 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 two last weeks of the intervention, Figure 3). From these measurements, we will measure 24 h glycaemic control, 3 h postprandial glucose levels (AUC) for the first meal of the day and nocturnal glycaemic control. The CGM monitors will be covered for the participants, so they will not be able to read 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).

*Blood sampling and biochemistry*

In addition to glucose and HbA1c (outlined above), analysis of fasting venous blood samples will include measurements of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. 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 and stored for later analyses. These later analyses will include, but are not limited to, insulin concentrations.

*Cardiorespiratory fitness and maximum heart rate*

Peak oxygen uptake ($VO_2$peak) will be measured using indirect calorimetry (MetaMax II Portable CPX System, Cortex, Germany). Participants will walk or run on a treadmill until voluntary exhaustion. Criteria for attainment of $VO_2$peak will be a leveling off in $O_2$-uptake, respiratory exchange ratio > 1.10 and/or volitional exhaustion.[26] We will use an individualised protocol where the test starts after a 10-minute warm up and where we increase the speed or inclination every 1-2 minutes, by 0.5-1.0 km/h or 1-2%. $VO_2$peak will be calculated as the highest consecutive 30 sec measured and reported as both absolute (L/min) and relative (mL/min/kg) values. We will record heart rate during these exercise tests and use the peak heart rate recorded during the test as an estimate of maximum heart rate.[27]

*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 minutes. We will report the average of three measurements taken one minute apart.

*Physical activity, sleep and diet*

Physical activity levels, energy expenditure and sleep will be estimated using activity monitors (Sensewear Armbands, BodyMedia, Pennsylvania, USA) during the same two 14-days periods as they will wear CGMs (Figure 3). Participants will fill out questionnaires about physical activity levels (International Physical Activity Questionnaire), sleep

(Pittsburgh Sleep Quality Index), and chronotype (Hornestberg Morningness Eveningness Questionnaire). They will complete an electronic food diary (www.kostholdsplanleggeren.no) during the 14-days periods at the start and the end of the trial (Figure 3). During the same periods, they will rate their hunger and satiety in the morning (before breakfast) and evening (just before going to bed) using 10 cm 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 h time window for energy intake. For HIT, adherence will be recorded as the number of HIT sessions the participants complete divided by the number of scheduled sessions, as well as the percentage of HR maximum during the HIT sessions.

*Adverse effects*

We will 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 restrictions in the use of our laboratories on 12.03.2020, we had completed all assessments from 40 participants. Participants who were randomised and baseline tested when the laboratories had to close 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. Some participants were randomised but had not yet started the intervention at the time of lab closure. For these participants, we will only collect data from the baseline week (monitoring) and wait until the lab reopens before the intervention starts. When the lab reopens, we will consider if we need to do another baseline assessment of these participants, based on their individual responses to how the Corona situation influenced their diet, physical activity, sleep and body weight. If the lab will be closed for more than two months, we will do new baseline assessments on all these participants. We will offer participants allocated to HIT at the time of lab closure, and who had already started their training, to continue supervised training as outdoor uphill walking/running or advise them to complete the sessions

un-supervised. Also for these participants, we will record the number of sessions completed and the relative exercise intensity using heart rate monitors.

**Sample size and statistical analysis**

*Sample size*

We calculated sample size based on a previous study on HIT for 6 weeks in overweight reproductive-aged women, where they reported an improvement of -54 (SD 64 mmol/L) in glucose AUC.[23] To detect such a difference between the HIT group and the control group, with a statistical power of 80% and an alpha level of 0.05 (two-sided), we need to have at least 24 participants in each of these groups. The power calculation is based on an independent t-test (two-sided) between these two groups, as there is insufficient data to guide a power calculation for the comparison between all four groups (i.e. not data on the effects of TRE and/or the combination of TRE and HIT in this population). However, in our analyses we will compare all four groups. We will include 116 participants to this study, 29 in each group, allowing for an expected 15% drop out, and will consider including more participants in the trial when we know how many will drop-out and will have missing data because of the COVID-19 situation.

*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 h on 5 or more days (on average) throughout the intervention period, whereas women assigned to HIT will be included if they have completed ≥ 16 training sessions at an intensity of ≥ 85% of HR maximum. We will use mixed linear 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 and colleagues.[28] P-values < 0.05 will be considered significant for both the primary and secondary outcome measures. However, due to multiple hypotheses, p-values 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 our knowledge, this study will be the first to determine the combined effects of HIT and TRE on cardiometabolic health. Our hypothesis is that the combination of these two interventions will induce synergistic effects on a range of health outcomes in reproductive-aged women with overweight/obesity. We believe that it will be feasible for the participants in our study to adhere to both HIT and TRE for 7 weeks and that these interventions could be viable alternatives to current exercise-nutrition recommendations for this population.

To our knowledge, there are only two previous studies on the combination of TRE and exercise training in humans.[29 30] Both these investigations determined whether TRE could have an additive effect to resistance training on body composition in healthy men. Moro and colleagues[29] showed that participants who undertook TRE in addition to resistance training decreased total body mass and fat mass, compared to the participants randomised to

resistance training only. Tinsley et al[30], on the other hand, showed no additional effect of TRE added to a resistance training program on body composition. In both these studies they have 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 HIT intervention in this study had to be stopped/modified in March 2020. This will have some consequences for the number of dropouts, missing data and timeline of the study. Some of the participants who were included, but not yet completed, when new restrictions about working from home and shut-down of gyms were enforced will likely change their physical activity and dietary habits because of the new regulations. Due to this, we may need to include more participants than originally planned 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. The main reason for including this delayed treatment is that it will act as a motivational factor for those allocated to the control group, enhancing the likelihood for them coming in for assessments after the initial 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 (i.e. contamination).

There is a great need for effective and feasible diet-exercise strategies for reproductive-aged women with poor metabolic health. If proven beneficial, the interventions we are assessing could relatively easily be implemented among women who are planning a pregnancy and who wish to optimise their metabolic health before conception. This will not only have immediate benefits for their own health but also positively influence their offspring's susceptibility to cardiometabolic diseases.

## TRIAL STATUS

Per 01.05.2020, we had included 67 women to this trial. Inclusion of new participants is stopped until the university laboratories will re-open.

## COMPETING INTERESTS

None of the authors has any conflicts of interest.

## AUTHORS' CONTRIBUTIONS

T.M. drafted the manuscript. T.M, C.S., and S.L. conceived and contributed to the design of the study and to the plan for analyses. T.M and C.S 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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## FIGURE LEGENDS

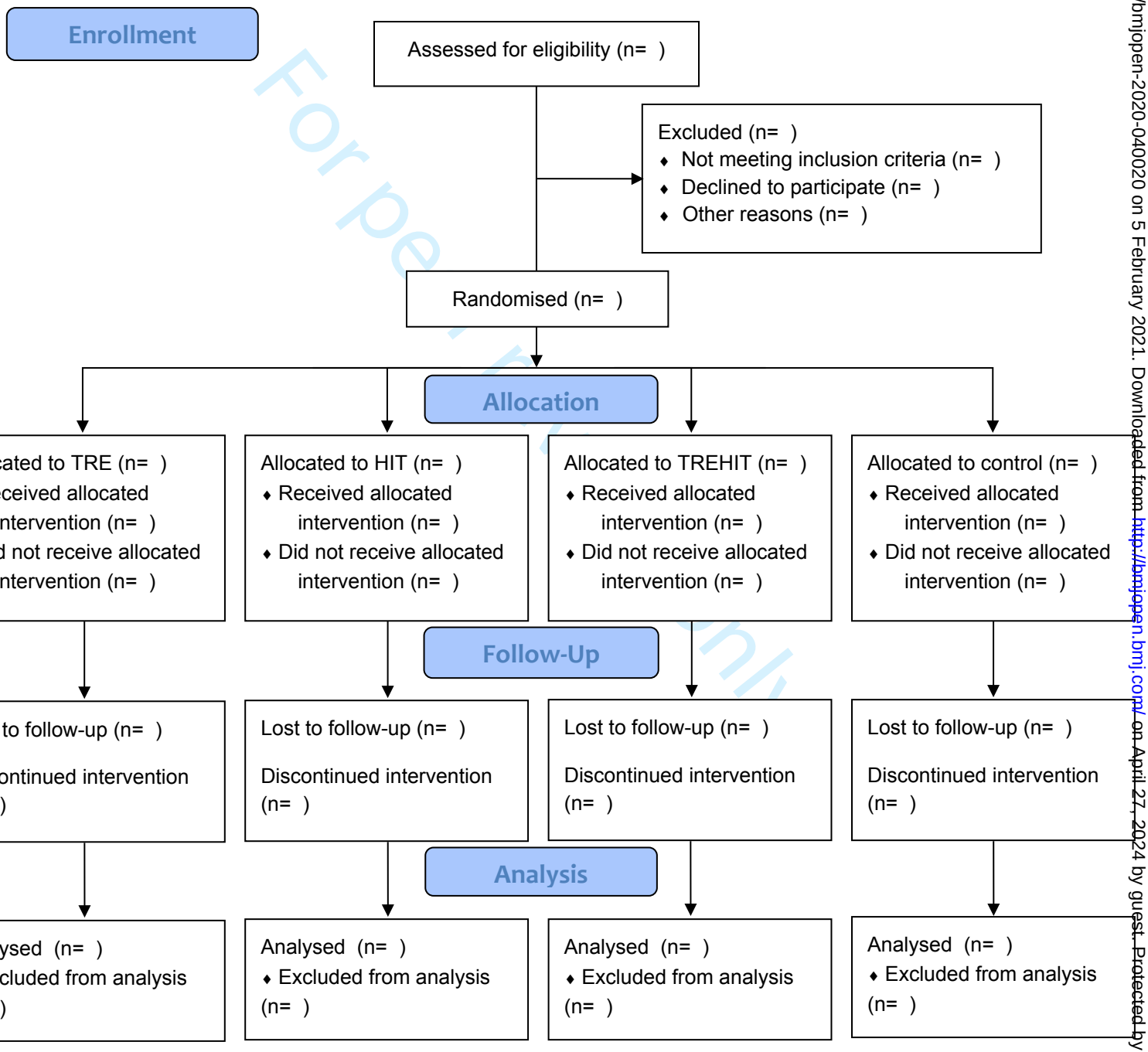
**Figure 1. CONSORT flow diagram.**

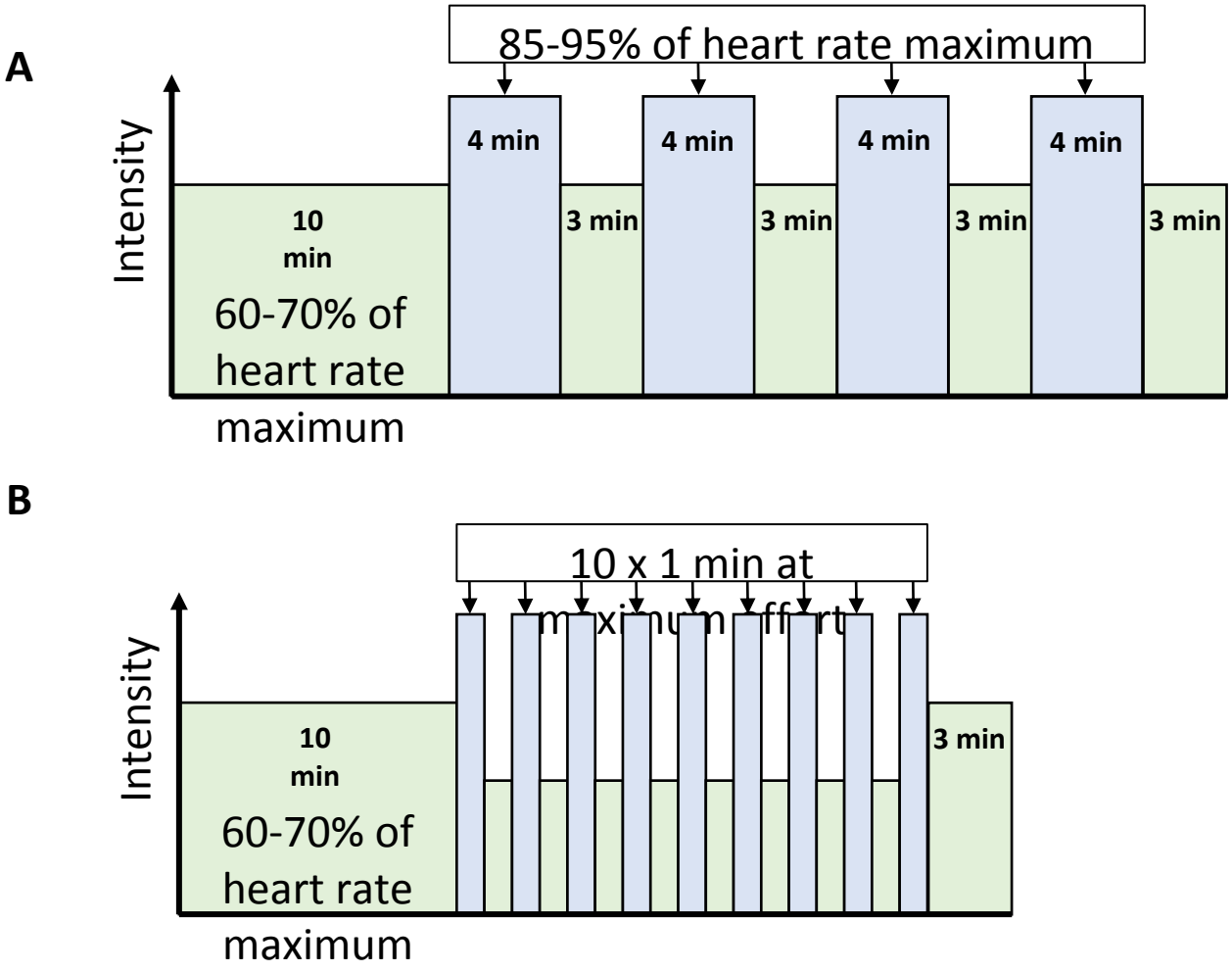
**Figure 2. High intensity interval training (HIT) protocol.** A) Two weekly sessions will be 4x4 min HIT; four 4-min work-bouts at 85-95% of heart rate maximum, separated by 3 min recovery at 60-70% of heart rate maximum. B) One weekly session will be 10 x 1 min HIT; ten 1-min work-bouts at the maximum intensity the participants can sustain, separated by 1-min low-intensity activity.

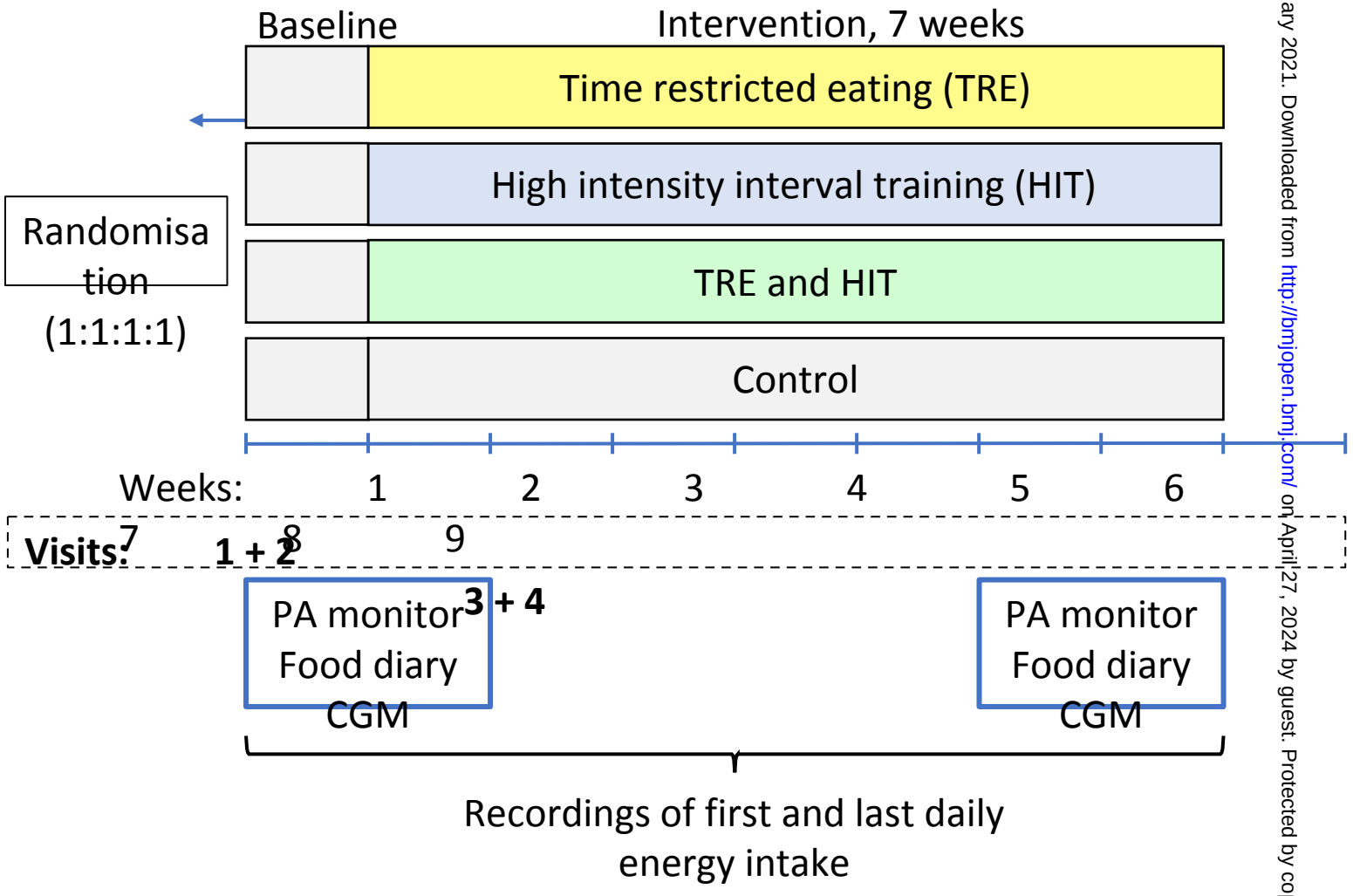
**Figure 3. Experimental design.** PA = Physical activity, CGM = Continuous glucose monitoring.

CONSORT
TRANSPARENT REPORTING of TRIALS

# CONSORT 2010 Flow Diagram







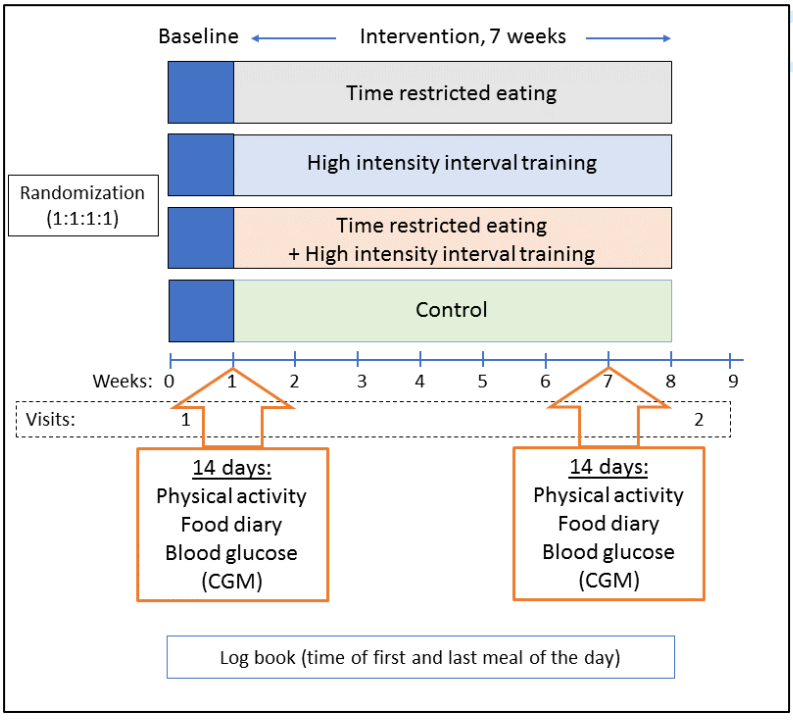
INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

# HIGH INTENSITY INTERVAL TRAINING AND TIME RESTRICTED FEEDING

You are invited to participate in a research project that will assess effects of high intensity interval training and so-called time restricted feeding on blood glucose control among women with a body mass index (BMI) of 27 kg/m$^2$ or more. Participants must be between 18 and 45 years of age and have a time-window of 12 hours or more for when they usually eat during the day (meaning that it is usually 12 hours or more between your first and last meal of the day). You also have to be able to walk or run on a treadmill or ride on a bike ergometer for at least 60 minutes and not exercise with high intensity more than once per week. You must understand written and oral English or Norwegian. The project is undertaken at NTNU.

## WHAT IS THE PROJECT ABOUT?

In this project, we will measure your blood glucose levels, insulin and lipids in the blood, body composition, physical fitness and blood pressure at the beginning of the project and again after eight weeks. You will also be asked to complete some questionnaires (about physical activity and sleep). You have to come in to the laboratory on two separate days for an assessment visit at the beginning of the study and again after 8 weeks. The assessments last about 2.5 hours on one of these days and about 40 min on the other day, at both the beginning and at the end of the study period. On one of the days, you will have to come in to the laboratory fasted in the morning, both at the beginning and at the end of the study period. Participants will be randomly allocated to one of four groups (see the figure below). One of the groups shall reduce their daily time-window of energy intake to a maximum of 10 hours per day for seven weeks. The second group shall also restrict their time-window for daily energy intake to a maximum of 10 hours per day and in addition complete three weekly sessions of high-intensity interval training per week. The third group shall perform three weekly session of high-intensity interval training per week. The exercise sessions will be supervised and take place at our laboratory at St. Olavs Hospital and you can choose what time of day you will like to come in. The last group will be a control group that will continue their usual activities and habitual time-window for energy intake (see figure below).



Participants allocated in this control group will after the initial seven weeks of the study be offered a delayed treatment where they can choose which of the three intervention protocols they want to follow (either time-restricted eating, high intensity interval training or both). These participants will get the same support and supervision for seven weeks after the second tests as the other participants get.

We will collect and record data about you in the project. This includes: age, height, body weight, body composition (the amount of muscles and body fat), your physical activity level (by questionnaires and by a physical activity monitor), blood pressure, results from blood analyses, physical fitness and continuous glucose monitoring. You will be asked to record your hunger and satiety and the time-window for daily energy intake. We will fit you with a continuous glucose monitor which is a little sensor that is inserted with a small needle on your upper arm. This sensor records your blood glucose automatically and stores it. We ask you to have this sensor on for two weeks in the beginning of the project period and two weeks at the. During these two two-week periods, we will also fit you with an activity monitor in the form of an armband on your upper arm and will be asked to record your diet in an online diet diary or on paper. During the whole study period, we ask you to record the time for your first and last meal of the day. We will sample blood where we will measure blood glucose and lipids. Additionally, we will sample blood that we will freeze for later analyses (of insulin and other markers of metabolism). We ask for permission to store some of this blood for later analyses that are not decided upon but are likely to include other markers of inflammation and appetite hormones. You will have to come in fasted on the testing days, meaning that you have not eaten or drunk anything but water since 22:00 the night before. After initial blood sampling, you will get to drink a solution of glucose (sugar) dissolved in water and we will sample blood every 30 min for analyses of how your body responds to this. We will measure your physical fitness by testing your maximum oxygen uptake on a treadmill test. This involves that you walk or run until exhaustion while breathing in a special mask. We will increase the speed or inclination of the treadmill in order to complete this test in 10-15 minutes.

## FORESEEABLE BENEFITS AND PREDICTABLE RISKS AND BURDENS OF TAKING PART

The benefits of taking part in this project are that you will get information about your blood glucose control, your blood pressure, body composition and physical fitness. We also think that it will be beneficial for your overall health to get supervised exercise training for a period and to restrict the time-window of daily energy intake. We see no major burdens of taking part apart from potential discomfort you might feel from the blood sampling and insertion of the blood glucose sensor.

## VOLUNTARY PARTICIPATION AND THE POSSIBLITY TO WITHDRAW CONSENT

Participation in the project is voluntary. If you wish to take part, you will need to sign the declaration of consent on the last page. You can, at any given time and without reason withdraw your consent. If you decide to withdraw participation in the project, you can demand that your tests and personal data concerning health be deleted, unless however, the personal data concerning health and tests have already been analysed or used in scientific publications. If you at a later point wish to withdraw consent or have questions regarding the project, you can contact Trine Moholdt by phone: 97098594 or e-mail: trine.moholdt@ntnu.no.

## WHAT WILL HAPPEN TO YOUR PERSONAL DATA CONCERNING HEALTH?

Any personal data concerning health that has been recorded about you will only be used as described in the purpose of the project. You have the right to access information that has been recorded about you and the right to stipulate that any error(s) in the information that is recorded is/are corrected. You also have the right to know which security measures have been/will be taken when your personal data concerning health is processed.

All information will be processed and used without your name or personal identification number, or any other information that is directly identifiable to you. A code links you and your personal data concerning health via an identifier list. Only Trine Moholdt and the collaborators in this project will have access to this list. If you agree to

participate in the study, you agree also to us transferring un-identifiable information about you to collaborating researchers at the Australian Catholic University in Melbourne, Australia. The list that can identify you will be kept in Norway at all times. Information about you will be anonymised or deleted five years after the project has ended.

## WHAT WILL HAPPEN TO THE BLOOD SAMPLES YOU HAVE TAKEN?

The blood samples taken from you will be stored in a specific Research Biobank connected to Research Project. Trine Moholdt is responsible for this biobank. The samples will be physically stored at the Department of Circulation and Medical Imaging, NTNU.

The Research Biobank will terminate once the research project has ended.

## INSURANCE

Participant are covered by the Patient Injuries Act.

## FOLLOW-UP PROJECT

We might want to do a future follow-up project and ask for your permission to store your contact details in case we want to contact you at a later stage. You can choose to participate in the project without giving such permission.

## FINANCE

The expenses of the project will be covered by NTNU as well as from a Novo Nordisk Foundation Challenge Grant. Participation in the project is free of charge.

## APPROVAL

The Regional Committee for Medical and Health Research Ethics has reviewed and approved the Research Project (REK 2019/851)

In accordance with the General Data Protection Regulation, the controller NTNU and the project manager Trine Moholdt are independently responsible to ensure that the processing of your personal data concerning health has a legal basis. This project has legal basis in accordance with the EUs General Data Protection Regulation, article 6 no. 1a, article 9 no. 2a and your consent.

You have the right to submit a complaint on the processing of your personal health data concerning health to the Norwegian Data Inspectorate (Datatilsynet).

## CONTACT INFORMATION

If you have any questions regarding the research project, you can get in touch with Trine Moholdt, 97098594, trine.moholdt@ntnu.no.

You can also get in touch with the Institution's Data Protection Officer (personvernombud) if you have any questions related to the use of your personal health data concerning health in the research project. NTNU's Data Protection Officer is Tomas Helgesen, 93079038, personvernombud@ntnu.no.

## I CONSENT TO PARTICIPATING IN THE RESEARCH PROJECT AND THAT MY PERSONAL DATA CONCERING HEALTH AND BIOLOGICAL MATERIAL CAN BE USED AS DESCRIBED ABOVE

*Please check one of the boxes below:*

*I **approve** that my contact details can be kept if the researchers wish to contact me for follow-up studies:* ☐

*I **do not approve** that my contact details can be kept if the researchers wish to contact me for follow-up studies:*

☐

---

City/Town and date

Participant's Signature

---

Participant's Name (in BLOCK LETTERS)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | 13 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,13 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-4 |
| | 6b | Explanation for choice of comparators | 3-4, 6, 12 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-7, 12 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5-6 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5-6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5-6 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 11 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 7-9 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 11 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | _____ |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _____ |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 11 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 11 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 11 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 11 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary file |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 8 |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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| Primary Subject Heading: | Nutrition and metabolism |
| Secondary Subject Heading: | Public health, Sports and exercise medicine |
| Keywords: | PREVENTIVE MEDICINE, SPORTS MEDICINE, PUBLIC HEALTH, NUTRITION & DIETETICS |
| | |

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# 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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Word count: 3661



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 with body mass index ≥ 27 kg/m$^2$ 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 two 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.

**Abstract word count:** 260

**Trial registration number:** Clinical trial gov NCT04019860.

**Keywords:** exercise, physical activity, diet, insulin sensitivity, body composition, pregnancy



## 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 sec) work-bouts and a total time commitment of < 45 min per 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 obesity[18] 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 to traditional endurance training in individuals with obesity[15], making HIIT is 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 12-14 to ≤ 8-10 hours/day reduces obesity, inflammation and insulin resistance in both rodent models[22] 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/obesity[27] 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. The primary aim of this trial is therefore 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, 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 NextMove 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. A 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 (BMI) ≥ 27.0 kg/m$^2$
- 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
- Breastfeeding within 24 weeks of study commencement
- Known cardiovascular disease, type 1 or type 2 diabetes
- Currently taking anti-hypertension medication
- Currently taking glucose- or lipid lowering medication
- Habitual eating window < 12 hours/day
- Habitually performing HIIT more than once per week
- Body mass variation > 4 kg three 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 (T.M.) will be informed about the allocation results on screen and by e-mail 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.

### *Time-restricted eating*

Participants will be asked to reduce their daily time-window for energy intake to a maximum of 10 hours. They can chose when to begin their eating window but will be advised that the last meal should be completed before or at 2000 h. We will give participants no advice on what to eat/drink, nor about the total caloric 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/SMS/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 x 4 min HIIT and

one session will be 10 x 1 min HIIT (Figure 2). Participants will walk or run on a treadmill. If required (due to physical limitations, e.g. 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 minutes.

*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 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 one 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 two separate days at baseline and on

two 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 the participants to abstain from vigorous physical activity for ≥ 48 h 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 h 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 (iAUC; 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 h), 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 OGGT), 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 (HOMA-IR); fasting serum insulin in μU/mL x 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 two last weeks of the intervention, Figure 3). From these measurements, we will determine 24 h glycaemic control, 3 h postprandial glucose levels (AUC) for the first meal of the day and nocturnal glycaemic control. The CGM monitors 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 and stored for later analyses. These later analyses will include, but are not limited to, insulin concentrations.

*Cardiorespiratory fitness and maximum heart rate*

Peak oxygen uptake ($VO_2$peak) will be measured using indirect calorimetry (MetaMax II Portable CPX System, Cortex, Germany). Participants will walk or run on a treadmill until volitional exhaustion. Criteria for attainment of $VO_2$peak will be a levelling off in $O_2$-uptake, respiratory exchange ratio > 1.10 and/or volitional exhaustion.[35] 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 minutes, by 0.5-1.0 km/h or 1-2%. $VO_2$peak will be determined as the highest consecutive 30 sec measured and reported as both absolute (L/min) and relative (mL/min/kg) values. 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 minutes. We will report the average of three measurements taken one minute 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, macro nutrients, 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 10 cm 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 h 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 March 12. 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 un-supervised. 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 is insufficient data to guide a power calculation for the comparison between all four groups (i.e. not 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 to this study, 30 in each group, allowing for an expected drop out rate of 15%, and will consider including more participants in the trial when we know how many drop-out/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 h 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 ≥ 85% of HR maximum. We will use mixed linear 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 and colleagues.[38] P-values < 0.05 will be considered significant for both the primary and secondary outcome measures. However, due to multiple hypotheses, p-values 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 and colleagues[39] reported that participants who undertook TRE in addition to resistance training decreased total body mass and fat mass, compared to 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 (i.e. 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.

## TRIAL STATUS

Per 28.10.2020, we had included 119 women to this trial.

## COMPETING INTERESTS

None of the authors has any conflicts of interest.

## AUTHORS' CONTRIBUTIONS

T.M. drafted the manuscript. T.M, J.A.H, C.S., and S.L. conceived and contributed to the design of the study and to the plan for analyses. T.M and C.S 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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## FIGURE LEGENDS

**Figure 1. CONSORT flow diagram.**

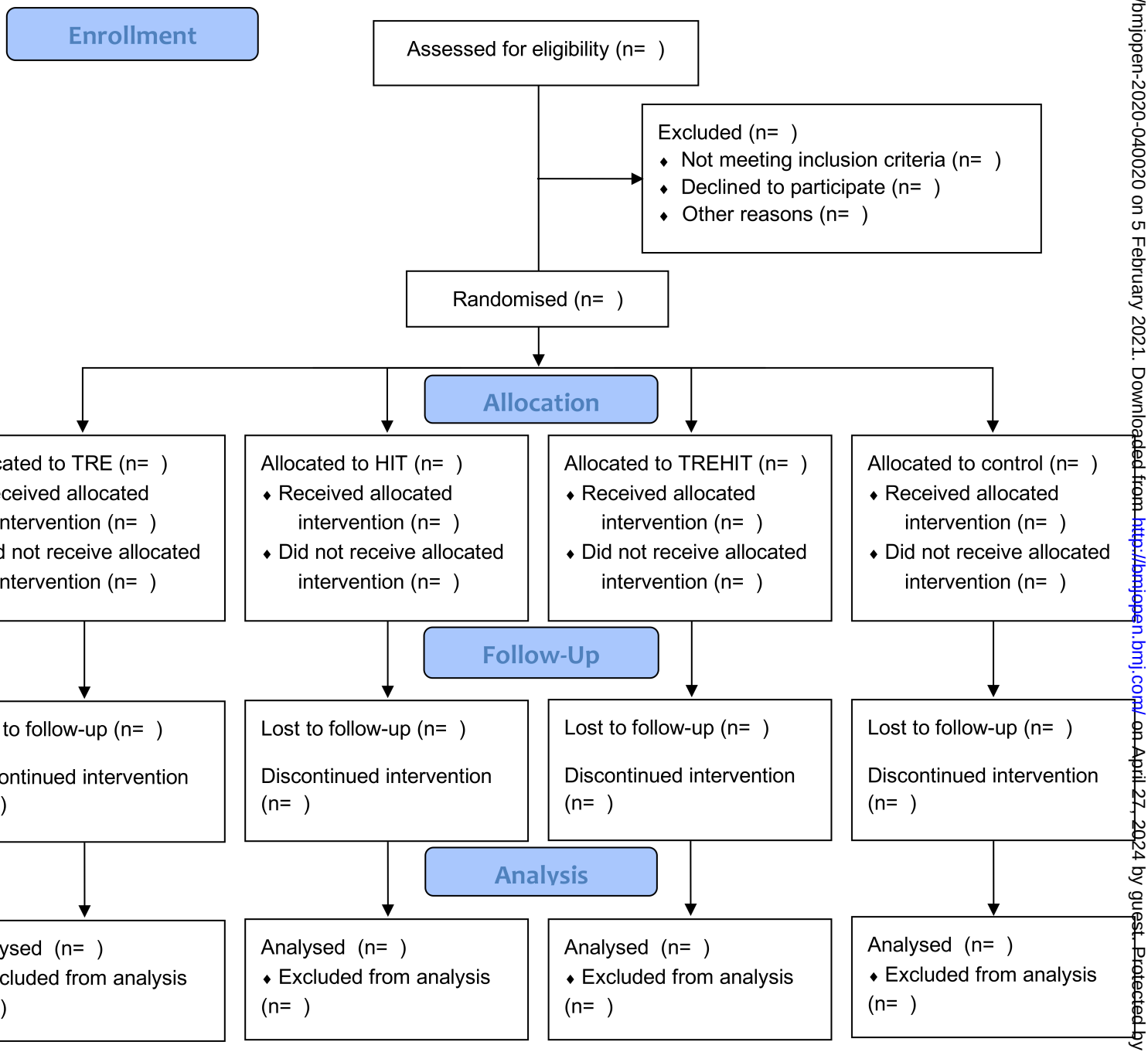
**Figure 2. High intensity interval training (HIIT) protocol.** A) Two weekly sessions will be 4x4 min HIIT; four 4-min work-bouts at 85-95% of heart rate maximum, separated by 3 min recovery at 60-70% of heart rate maximum. B) One weekly session will be

10 x 1 min HIIT; ten 1-min work-bouts at the maximum intensity the participants can sustain, separated by 1-min low-intensity activity.

**Figure 3. Experimental design.** PA = Physical activity, CGM = Continuous glucose monitoring.

CONSORT
TRANSPARENT REPORTING of TRIALS

# CONSORT 2010 Flow Diagram



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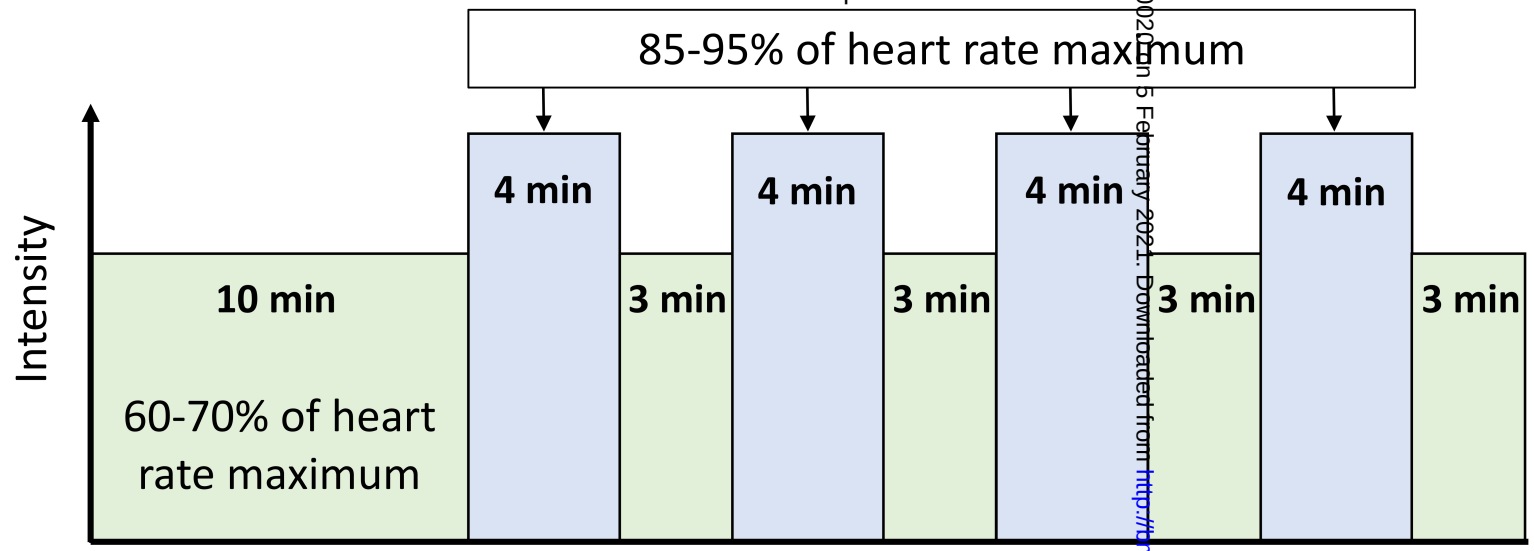
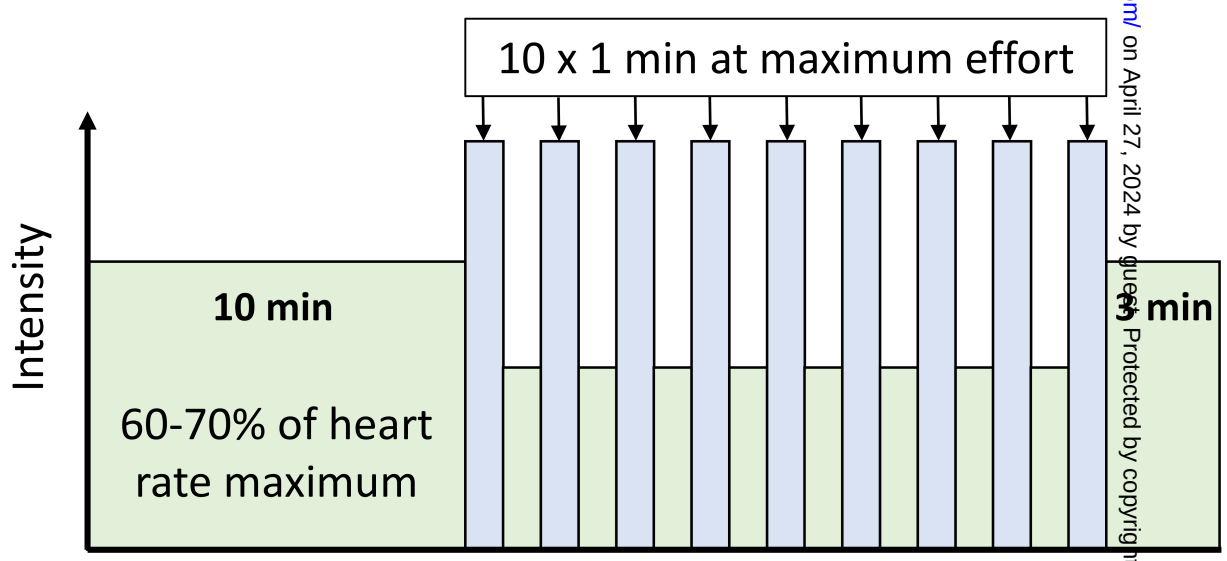
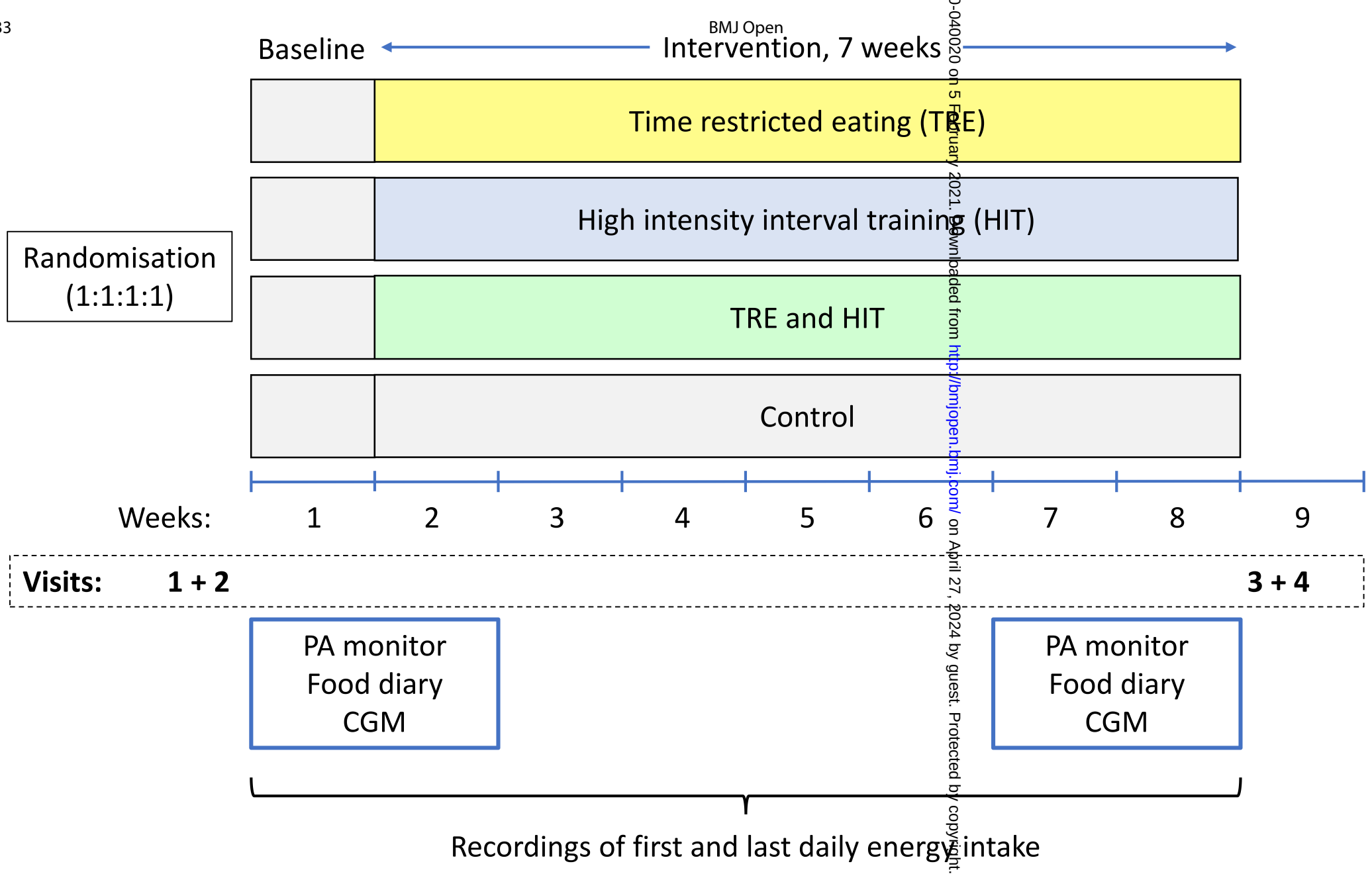



B






SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | 13 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1,13 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |

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| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3-4 |
| | 6b | Explanation for choice of comparators | 3-4, 6, 12 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6-7 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-7, 12 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7-9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |

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|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 5-6 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 5-6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 5-6 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 11 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 7-9 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 10 |

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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 11 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 10 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | _____ |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | _____ |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 11 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 11 |

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| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 11 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 11 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | 13 |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supplementary file |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | 8 |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.