Trials

STUDY PROTOCOL

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Comparison of morning vs evening exercise on weight loss and related health behaviors in individuals with overweight or obesity: study protocol for a 56-week randomized controlled trial (TIMEX)

Seth A. Creasy[1,2], Katrina M. Oselinsky[1,2*], Erik A. Willis[3], Ann E. Caldwell[1,2], Rebecca Rosenberg[2], Danielle M. Ostendorf[5], Shelby Panter[1,2], Liza Wayland[1], Kristen Bing[1], Justin Lorentzen[1], Matthew Breit[1,2], Kevin Clark[1], Anaeli Sandoval[1], Joseph E. Donnelly[4], Edward L. Melanson[2] and Victoria A. Catenacci[1,2]

Abstract

Background Aerobic exercise is recommended for weight management. Recent evidence suggests that there may be time-dependent differences in how exercise affects body weight and energy balance regulation. The primary purpose of this study is to determine the effect of morning versus evening aerobic exercise on changes in body composition and components of energy balance in adults with overweight and obesity.

Methods The Timing Intervention of Morning versus Evening EXercise (TIMEX) study is a two-arm, 56-week, block randomized (1:1) aerobic exercise intervention. One hundred twenty-eight adults with overweight and obesity will be randomized to engage in morning (AM-Ex, 06:00–10:00) or evening (PM-Ex, 15:00–19:00) moderate- to-vigorous intensity aerobic exercise progressing to 2000 kcal/week of energy expenditure. The primary outcome is change in body weight at 7 months. Secondary outcomes include changes in body composition, energy intake, hunger and eating behaviors, energy expenditure, and physical activity behaviors at 7 and 13 months.

Discussion Aerobic exercise elicits modest weight loss; however, there is substantial inter-individual variability in the weight loss response with some individuals losing significant amounts of weight and others gaining weight. The time of day exercise is performed may contribute to this weight loss variability. Understanding how the time of day of exercise affects weight loss and components of energy balance may lead to tailored exercise interventions that enhance weight loss. The TIMEX study will determine the effect of a guidelines-based dose of aerobic exercise completed in the morning versus the evening on weight loss, energy intake, and energy expenditure.

Trial registration ClinicalTrials.gov NCT02153252. Registered on 12/10/2021.

Keywords Exercise timing, Weight loss, Obesity, Randomized trial, Energy balance, Energy intake, Energy expenditure

*Correspondence:
Katrina M. Oselinsky
oselinskyk@gmail.com
Full list of author information is available at the end of the article

Introduction

Background and rationale {6a}

Exercise alone (i.e., without dietary intervention) is not generally recommended for weight loss [1, 2]. However, this is based on studies with insufficient exercise prescriptions resulting in minimal mean weight loss (1–3 kg) [3–5]. Several studies have shown that higher amounts of exercise (≥2000 kcal/week) result in clinically meaningful (≥5%) weight losses in both men and women [6–8]. However, regardless of exercise dose, there is substantial inter-individual variability in weight loss response to exercise interventions. Well-designed, long-term (≥6 months) studies have consistently shown that weight loss induced by exercise is significantly less than expected based on the measured EE of the exercise sessions [3, 4, 6, 9–12]. Exploration of factors which contribute to the variability in weight loss response to exercise is an important research priority [10, 13]. Prior studies suggest that the time of day that exercise is performed may contribute to the variability in weight loss response.

It has been hypothesized that the time of day of exercise may alter energy balance and compensatory responses to exercise differentially, thereby introducing variability to the weight loss response. This hypothesis is supported by observational findings suggesting that engagement in morning physical activity is beneficial for weight management [14]. In addition, a secondary analysis of the Midwest Exercise Trial-2 (MET-2) [15] found that individuals who performed the majority of their exercise in the morning lost significantly more fat mass compared to individuals who performed the majority of their exercise in the evening, despite no differences in baseline characteristics, exercise adherence, and measured exercise energy expenditure (EE). In addition, that secondary analysis found that morning exercise may increase total EE and improve dietary intake compared to evening exercise, though the differences observed were not statistically significant. One subsequent, short-term (i.e., 15-week) study also found preliminary evidence that morning exercise increases total daily energy expenditure (TDEE) compared to evening exercise [16]. Another short-term (6-week) study found that morning exercise resulted in greater weight loss compared to evening exercise, and that this was driven by reductions in self-reported energy intake [17]. Not all studies agree with some demonstrating beneficial effects of morning exercise [15, 17, 18], others finding no differences between morning and evening exercise [16, 19–21], and others finding beneficial effects of evening exercise for weight management [22, 23]. These prior studies suffer from design limitations including non-randomization, small samples, short study durations, limited control of the exercise dose, and minimal study duration.

Thus, longer-term randomized trials are needed to evaluate the effect of exercise time of day on weight loss and compensatory responses. In addition, there is a need to rigorously control the exercise dose (time of day, intensity, duration, etc.) and utilize an exercise prescription that is aligned with current recommendations for weight loss. The *T*iming *I*ntervention of *M*orning versus *E*vening *EX*ercise (TIMEX) study was designed to compare the effect of morning versus evening aerobic exercise progressing to 2000 kcal/week on weight loss at 30 weeks (primary endpoint) and 56 weeks in adults with overweight or obesity. The study will generate novel data on the clinical effectiveness of exercising at different times of the day, which is of significant interest to the general population. In addition, this study will utilize rigorous objective methods to examine how exercise time of day affects energy balance (i.e., energy expenditure and energy intake).

Objectives {7}

The aims of TIMEX are to (1) compare the effects of morning exercise (AM-Ex) vs. evening exercise (PM-Ex) on changes in body weight (primary outcome) and body composition, (2) compare the effects of AM-Ex vs PM-Ex on changes in energy intake (EI) and appetite, and (3) compare the effects of AM-Ex vs PM-Ex on changes in energy expenditure (EE), non-exercise physical activity (PA), and sedentary time. Informed by our prior post hoc analysis of a supervised, exercise-only intervention performed in adults with overweight or obesity in which we found morning exercisers lost significantly more weight compared to evening exercisers, our a priori hypothesis is that AM-Ex will result in greater weight loss (primary outcome) and greater decreases in fat mass at 30 weeks (primary endpoint) compared to PM-Ex. Based on preliminary data which suggests AM-Ex may limit the development of compensatory changes in EI and/or EE, we also hypothesize that AM-Ex will attenuate increases in hunger and food cravings and result in a lower overall increase in EI compared to PM-Ex, and that AM-Ex will attenuate decreases in non-exercise physical activity, attenuate increases in sedentary time, and result in a greater overall increase in TDEE compared to PM-Ex. Finally, we will explore the effects of AM-Ex vs PM-Ex on changes in meal timing and sleep timing and examine their association with changes in weight, EI, and EE to provide insight on how consistent exercise timing may shift circadian-related cues known to affect body weight regulation.

Trial design {8}

TIMEX is designed as a two-arm randomized controlled trial. Eligible participants will be randomized into one

of two study arms: AM-Ex or PM-Ex. Both groups will receive a 30-week supervised aerobic exercise intervention progressing to 2000 kcal/week. Upon completion of the supervised exercise phase, participants will be asked to maintain this level of exercise during their randomized AM or PM exercise windows for the following 26 weeks, but exercise will no longer be supervised. This study was powered as a superiority trial with differences between the AM-Ex and PM-Ex groups in weight change (kg) at 30 weeks as the primary endpoint. The primary analyses will be performed according to intent-to-treat (ITT) principles and followed by sensitivity analyses including a completer's analysis and a per-protocol analysis (participants with ≥ 75% adherence to supervised exercise). There are no planned interim analyses. Outcome measures will take place at baseline (week 0) and weeks 15, 30, and 56.

Methods: participants, interventions, and outcomes

Study setting {9}

Participants will be recruited from the greater Denver metro area and studied at a single site, the University of Colorado Anschutz Medical Campus (CU AMC), which is located in the USA. Exercise will take place at the CU AMC Anschutz Health and Wellness Center (AHWC), a 30,000 square foot state-of-the-art exercise facility. Additional study procedures will be performed at the AHWC Clinical Research Center, the Clinical Translational Research Center (CTRC) outpatient clinic, and the UCHealth University of Colorado Hospital (UCH).

Eligibility criteria {10}

Participants will be included in this trial if they are 18–55 years old, have a body mass index (BMI) between 25 and 40 kg/m^2, are physically inactive (defined as self-reporting < 150 min of moderate to vigorous intensity PA per week over the past 3 months), live or work within 30 min of the AHWC, and have no contraindications to exercise or limitations on ability to be physically active. Participants will be excluded if they have the following:

(1) Plans to move out of the Denver area during the study intervention.
(2) Plans for extended travel (> 2 weeks continuous travel) during the study intervention.
(3) Diastolic blood pressure > 100 mm HG or systolic blood pressure > 160 mm HG.
(4) Resting heart rate > 100.
(5) Diabetes (fasting glucose ≥ 126 mg/dL or hemoglobin A1C ≥ 6.5%).
(6) Undiagnosed hypo- or hyperthyroidism (TSH outside of the normal reference range) or history of uncontrolled thyroid disorder.
(7) Clinically significant abnormalities in hematocrit, white blood cell count, or platelets.
(8) Triglycerides > 400 mg/dL.
(9) LDL cholesterol > 200 mg/dL.
(10) Abnormal resting electrocardiogram.
(11) The presence or history of any metabolic or chronic health problems which would affect appetite, food intake, energy metabolism, or the ability to optimally participate in the exercise component including the following: peripheral vascular disease, cerebrovascular disease, significant cardiac arrhythmias or cardiac valve disease, cancer (within the last 5 years, except skin cancer or other cancers considered cured with excellent prognosis), human immunodeficiency virus infection, significant renal, musculoskeletal, neurologic, hematologic, or psychiatric disease.
(12) Significant gastrointestinal disorders (Crohn's disease, ulcerative colitis, chronic diarrhea, or active gallbladder disease).
(13) Significant pulmonary disorders (chronic obstructive pulmonary disease, interstitial lung disease, cystic fibrosis, or uncontrolled asthma).
(14) Symptoms suggestive of cardiovascular disease (chest pain, shortness of breath at rest or with mild exertion, and syncope).
(15) Regular use of prescription or over-the-counter medications known to significantly impact appetite, weight, sleep, or energy metabolism (e.g., appetite suppressants, lithium, stimulants, antipsychotics, and tricyclic antidepressants).
(16) Use of medications that would impact ability to achieve age-predicted maximum heart rate (e.g., beta blockers and cardio-selective calcium channel blockers).
(17) Regular use of systemic glucocorticoids.
(18) Regular use of obesity pharmacotherapeutic agents within the last 6 months.
(19) Previous obesity treatment with surgery or weight loss device, except (a) liposuction and/or abdominoplasty if performed > 1 year before screening; (b) lap banding if the band has been removed > 1 year before screening; (c) intragastric balloon if the balloon has been removed > 1 year before screening; (d) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening; or (e) AspireAssist or other endoscopically placed weight loss device if the device has been removed > 1 year before screening.

(20) Current alcohol or substance abuse.
(21) Nicotine use in the past 6 months.
(22) History of clinically diagnosed eating disorders including anorexia nervosa, bulimia, and binge eating disorder.
(23) Current severe depression or history of severe depression within the previous year, based on the *Diagnostic and Statistical Manual of Mental Disorders IV* text revision criteria for major depressive episode.
(24) History of other significant psychiatric illness (e.g., psychosis, schizophrenia, mania, bipolar disorder).
(25) Night-time shiftwork, rotating work, irregular sleep/wake patterns, or other scheduling constraints which may hinder ability to consistently exercise at specific times of the day.
(26) Urinary incontinence or retention (as per principal investigator's [PI] discretion based on whether degree of incontinence/retention may impact doubly labeled water measures).
(27) Weight loss > 5% in the past 3 months.
(28) Weight gain > 10% in the past 3 months requires assessment by PI to determine reason for weight gain and if it is appropriate for the participant to participate in the study.
(29) Weight loss of > 50 lbs in the past 3 years for any reason except postpartum weight loss requires assessment by PI to determine reason for weight gain and if it is appropriate for the participant to participate in the study.
(30) Currently participating in or planning to participate in any formal weight loss, dietary modification, or physical activity/exercise programs or clinical trials.
(31) Women who are currently pregnant, who have been pregnant in the past 6 months, are currently breastfeeding, or whom are planning pregnancy will be excluded. Women of childbearing potential who are sexually active with men may be enrolled if they have had a tubal ligation or use a reliable means of contraception during the study.

Who will take informed consent? {26a}

Participants will be recruited from the CU AMC and the Metro Denver Area through mass emails, mailings, flyers, and social media advertising. Following an online screening questionnaire to determine initial eligibility and provide an overview of the study, interested volunteers will be scheduled for an in-person screening visit. Prior to the in-person screening visit, the consent document will be emailed to the participant, and the participant will be asked to review the study consent form in an unhurried setting. Following independent review of the consent documents by the potential study participant, study staff will meet in person or virtually with the participant to explain and review the study consent form, to confirm the participant's understanding of the study, and to answer any questions that the participant might have. Once the participant demonstrates sufficient understanding of the study and study procedures and agrees to participate, the consent will be signed electronically or via pen and paper and returned to study staff. By signing the study consent form, participants agree to participate in the study intervention and to complete study assessments, to allow their data and specimen to be stored and used for future research, and to be contacted for future research studies unless otherwise requested in writing by the participant.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

NA. No additional consent provisions will be included. All participants will consent to the full protocol as proposed.

Interventions

Explanation for the choice of comparators {6b}

We chose to compare AM-Ex to PM-Ex as our preliminary data suggested that morning aerobic exercise may produce superior weight loss when compared to evening aerobic exercise. AM-Ex will perform all exercise during a specified window in the morning (06:00–10:00), while PM-Ex will perform all exercise in a specified window in the late afternoon/evening (15:00–19:00). A no-exercise control group was not utilized in this study as previous research has sufficiently demonstrated the health and weight loss benefits of exercise, and it is unethical to withhold treatment (i.e., exercise) from individuals with overweight or obesity.

Equating the exercise dose and merely shifting the time-of-day window of when the exercise will be performed permits us to compare the effect of exercise timing on weight loss and compensatory behaviors. Both groups will receive a time-and-attention matched behavioral support program to enhance adherence to the exercise prescriptions.

Intervention description {11a}

Exercise intervention

Both AM-Ex and PM-Ex will receive a 30-week supervised aerobic exercise program followed by a 26-week maintenance phase during which exercise is unsupervised. AM-Ex will perform all exercise in the morning (06:00–10:00), while PM-Ex will perform all exercise in

the late afternoon/evening (15:00–19:00). Time of last meal will not be controlled but will be recorded for each exercise session. Participants will be instructed to eat *ad libitum* during the study to allow us to ascertain the differential impact of AM-Ex vs PM-Ex on energy intake and eating behaviors.

A 30-week supervised exercise phase (weeks 1–30) Three sessions per week will be supervised "on- site" at the AHWC exercise facility to ensure treatment fidelity and provide accountability and support for exercise. During on-site exercise sessions, study staff will periodically check in with participants to ensure they are adhering to the exercise prescription. Following on-site exercise sessions, study staff will verify and record exercise data and provide the participant feedback if necessary. One session per week will be "on-own" to allow flexibility and enhance adherence to the high volume of exercise. On-own exercise sessions may consist of any form of aerobic activity as long as heart rate (HR) is at the prescribed target. All exercise sessions, including on-site and on-own, will be performed within the randomized AM or PM window and monitored electronically using HR monitors (Polar H10, Polar Electro Inc., Kempele, Finland). The Polar H10 connects via Bluetooth to AHWC exercise equipment and the Polar Beat phone application and transmits exercise data (date/time, mean HR, duration) to a secure, central database that can be checked by study staff in real time to ensure adherence to prescribed exercise. The exercise dose will progress from 750 kcal/week of exercise EE to 2000 kcal/week of exercise EE over the initial 20 weeks of the supervised exercise program in accordance with American College of Sports Medicine (ACSM) guidelines [24] (see Table 1).

Because exercise will be based on individual exercise EE, participants will exercise for different durations. Based upon data from MET-2, we anticipate average exercise duration to achieve the target 2000 kcal/week in four exercise sessions (500 kcal/session exercise EE) will be ~ 60 min/session for females and ~ 45 min/session for males. Target exercise intensity will progress from 70 to 80% of maximal heart rate (MHR) and will be tightly controlled to avoid any differential effect of exercise intensity on outcomes of interest. Exercise EE will be tested and calibrated four times during the 30-week supervised exercise phase to adjust for training adaptations. Participants will have their choice to exercise on six different pieces of aerobic exercise equipment: treadmill, elliptical, stationary cycle, recumbent cycle, rowing machine, and stair stepper. At least 50% of exercise minutes will be treadmill based. At week 15, participants will be allowed to perform two on-site supervised and two on-own sessions per week. At week 21, participants with prescriptions > 60 min/session will be given the choice to complete their exercise across five sessions/week to reduce exercise session duration. On-site and on-own exercise session data will be reviewed by study staff weekly, and adherence reports will be emailed to participants every 2 weeks. The exercise ramp-up may be adjusted based on participant feedback and exercise adherence. If adjustments to the ramp-up are made, they will be applied equally to both groups within a cohort (i.e., the ramp-up will remain identical for AM-Ex and PM-EX).

Exercise prescriptions may be adjusted on a per participant basis in the event of illness or injuries.

A 26-week maintenance phase (weeks 31–56) Exercise prescriptions will remain at 2000 kcal/week, and

Table 1 Description of exercise ramp-up

Study week	Sessions/week	Exercise intensity (%Hrmax)	Exercise prescription (kcal/session)	Total exercise prescription (kcal/week)
0	Establish fitness center membership, orientation			
1–2	3 supervised, 1 on-own	70%	187.5	750
3–4	3 supervised, 1 on-own	70%	250	1000
5–6	3 supervised, 1 on-own	75%	250	1000
7–10	3 supervised, 1 on-own	75%	312.5	1250
11–12	3 supervised, 1 on-own	80%	312.5	1250
13–14	3 supervised, 1 on-own	80%	375	1500
15–16	2 supervised, 2 on-own	80%	375	1500
17–20	2 supervised, 2 on-own	80%	437.5	1750
21–30*	2 supervised, 2 on-own	80%	500	2000
31–56*	4 on-own	80%	500	2000

* Option to split exercise into five sessions/week (e.g., three unsupervised, two on-own) if Rx was > 60 min. Hrmax, maximum heart rate; Rx, prescription

participants will be asked to continue to perform all exercise in their randomized AM or PM window. Intensity will remain at 80% MHR. Participants will be provided access to the AHWC exercise facility; however, exercise will no longer be supervised by study staff. HR monitors and the Polar app will continue to be used to track adherence to prescribed exercise.

Consideration of training response

We anticipate exercise training adaptations during the 30-week supervised exercise intervention (increased aerobic capacity and exercise efficiency) which will impact exercise EE (kcal/min). In addition, changes in body weight over the intervention will also impact exercise EE. Thus, submaximal exercise energy expenditure testing using indirect calorimetry will be performed four times during the 30-week supervised exercise intervention to adjust exercise prescriptions and ensure maintenance of the target EE per session.

Criteria for discontinuing or modifying allocated interventions {11b}

If participants experience fatigue or shortness of breath during the exercise sessions, they will be permitted to rest or reduce the exercise intensity to complete the prescribed exercise session. It is anticipated that some participants will experience soreness during the first few days of exercise, but we expect the symptoms will be minor and transient. If participants experience muscle soreness, they will be permitted to rest or reduce the exercise intensity to complete the prescribed exercise session, and we will prescribe light stretching and hot/cold therapy to reduce the soreness. If these approaches do not alleviate the soreness, we will advise the use of over-the-counter pain relievers (e.g., aspirin, acetaminophen, ibuprofen), unless contraindicated. Although some minor to moderate orthopedic injuries may occur during the exercise program (primarily lower body musculoskeletal overuse injuries such as tendonitis, shin splints, plantar fasciitis) given the gradual increase of the exercise prescription, we do not expect any severe orthopedic injuries. Participants who experience minor to moderate orthopedic injuries or intercurrent illness will be permitted to rest and allowed to remain in the study and return to exercise as tolerated. If participants are unable to safely return to exercise after an injury or illness, they will be withdrawn from the study. Strategies to minimize injury risk (including stretching and proper footwear) will be reviewed at the orientation session and reiterated during behavioral support sessions. Participants will not be permitted to switch randomized treatment groups (i.e., change from AM-Ex to PM-Ex or vice versa). The exercise interventions can be discontinued at any time at the participant's request, and they will be withdrawn from the study.

Strategies to improve adherence to interventions {11c}

Exercise behavioral support

Participants in both groups will receive theory-based behavioral support to promote exercise adherence and reduce attrition. Participants will receive approximately six group exercise support sessions and six individual exercise support sessions during weeks 1–56. These sessions will be held virtually, and randomized groups will meet separately. The exercise support sessions will follow a standardized curriculum developed by the study team to ensure both groups receive equivalent exposure. The curriculum is based on core principles and behavior change techniques used to support increases in PA in the Diabetes Prevention Program (DPP) [25]. The curriculum was designed using social cognitive theory [26] and includes several behavior change techniques identified by Michie [27] focusing specifically on shaping knowledge, goals and planning, time management, feedback and monitoring, associations, social support, and natural consequences (with an emphasis on the immediate benefits of exercise, e.g., reduced stress and improved mood). Sessions will be led by an interventionalist trained to focus on behavior change techniques proven to be effective for increasing PA in adults with overweight or obesity [28]. The behavioral support program (i.e., class content, frequency of meetings) may be adjusted based on participant feedback and exercise adherence. If changes are made, they will be applied equally to both groups within a cohort (i.e., will remain identical between AM-Ex and PM-Ex).

Additional strategies to enhance adherence and retention

The AHWC is equipped with interactive exercise equipment, televisions, music, water fountains, men's and women's locker rooms with sauna and steam room, showers, towel service, and amenities. Participants will have access to reserved exercise equipment during their designated workout time. Participants will be updated on their exercise adherence via email every 2 weeks to provide feedback and accountability. If participants are $\geq$ 85% adherent to their prescribed exercise minutes, they will receive a small payment (US $10) for completing exercise sessions every 2 weeks. We will also implement strategies to enhance adherence and reduce attrition in the event of illness, injury, travel, or life events (which are expected events during an exercise intervention of this duration). Participants will also be allowed to perform sessions on on-own during travel. Participants will be allowed to perform one make-up session per week in

the event of illness, injury, or travel. In the event of significant illness, injury, or life event, the exercise ramp-up will be adjusted, and the intervention will be extended accordingly.

Relevant concomitant care permitted or prohibited during the trial {11d}

During the intervention, participants will not be permitted to (1) participate in any other physical activity, exercise, nutrition, weight loss programs, or clinical trials, (2) engage in visits with a medical provider focused on weight loss, (3) use prescription or over-the-counter anti-obesity medications, or (4) undergo obesity treatment via bariatric surgery or endoscopic weight loss device placement.

Provisions for posttrial care {30}

In the event a participant experiences an injury or harm as a direct result of their participation in the study, no additional compensation will be provided. Participants will continue to have access to a printed version of the study materials provided during the intervention after their study participation concludes.

Outcomes {12}

Outcome assessments will be conducted at baseline (week 0) and at weeks 15, 30, and 56. The target windows for completing these measures were as follows (± 4 weeks for baseline and week 56, ± 2 weeks for weeks 15 and 30). This timeline supports the assessment of the primary and secondary outcomes and facilitates robust monitoring of intervention adherence and impacts. The primary study outcome is body weight, as measured in the clinic. Full outcome measure definitions are provided in Table 2.

Anthropometric measures

Participants will have their body weight measured in the morning after an overnight fast using a digital scale in the AHWC Clinical Research Center, accurate to ± 0.1 kg at baseline and weeks 15, 30, and 56. Participants will also be given a smart scale (BodyTrace Smart Scales, Palo Alto, CA, USA) for daily home weighing during the 56-week study. These weights will be transmitted via a wireless cellular network to a secure website. At baseline, height will be measured to the nearest 1 mm with a stadiometer in the clinic. Waist circumference (WC) will be measured to the nearest millimeter using a tape measure, parallel to the floor and just superior to the iliac crest, at baseline and weeks 15, 30, and 56. Blood pressure (BP) will be measured at baseline and weeks 15, 30, and 56 with an automatic sphygmomanometer (average of two seated readings) after 5 min of seated rest. Fat mass (FM) and fat-free mass (FFM) will be quantified using dual-energy X-ray absorptiometry (DXA) at the CU AMC CTRC at baseline, week 30, and week 56.

Resting energy expenditure (REE)

Resting energy expenditure will be measured in the morning in a thermoneutral (68–74 °F) quiet room using indirect calorimetry (Parvo Medics TrueOne 2400, Salt Lake City, UT, USA) at baseline and week 30 after a 12-h overnight fast and a 24-h abstention from exercise. Participants will lay down and rest quietly for 30 min before placing the transparent, ventilated hood over their heads. The participant will be instructed to remain motionless, awake, and relaxed and will be asked to breathe normally during the test. Before REE measurement, the pneumotach flowmeter will be calibrated using a 3-L calibration syringe (Hans Rudolph Inc., Shawnee, KS, USA), and gas analyzers will be calibrated using standardized gas mixtures. REE will be measured for a minimum of 20 min, and the average of 10 stable minutes of measurement will be used to calculate REE using the Weir Equation [55].

Free-living total daily energy expenditure (TDEE) and energy intake (EI)

Free-living total daily energy expenditure will be assessed using the doubly labeled water (DLW) method over 14 days at baseline and week 30. A 14-day measurement is preferred; however, this may be shortened to 7 days in certain circumstances due to holidays or participant travel. A baseline urine sample will be collected prior to administration of the oral dose of DLW containing $H2^{18}O$ (10% atom percent excess, APE) and $^{2}H2O$ (99.8% APE) mixed in a ratio of 15:1. Participants will consume a dose based on body weight and an estimation of total body water (~ 73% of FFM). Delivered doses will range from 0.96 to 1.23 g/kg of body weight for females and 1.05 to 1.38 g/kg of body weight for males at baseline. Delivered doses will increase slightly at week 30 to account for additional water turnover associated with exercise (ranging from 1.05 to 1.54 g/kg of body weight). The dosing container will be rinsed twice with 100 mL of water and the rinsing doses consumed. The exact time of dosing will be recorded, and urine samples will be collected 4 h and 5 h post-dose. Urine samples will be measured using off-axis integrated cavity output spectroscopy (OA-ICOS, Los Gatos Research Inc., Mountain View, CA, USA), as previously described [56]. Samples will be stored frozen at − 80 °C until analysis. Free-living total daily energy expenditure will be calculated using a standard equation [57]. Exercise EE will be calculated by multiplying the measured EE of exercise sessions using indirect calorimetry (kcal/min, see below) by the number of minutes of exercise completed each week. Non-exercise EE will be

Table 2 Outcome measurement definitions

Domain	Specific measurement	Specific metric	Method of aggregation	Time-point
Primary outcome				
Weight	Calibrated Digital Scale accurate to the nearest ± 1 mm	Change from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Secondary outcomes				
Anthropometric measures				
Height	Stadiometer, average of three consecutive measurements rounded to the nearest 1 mm	Mean at baseline	Mean	Week 0
Waist circumference	Tape measure, average of three consecutive measurements rounded to the nearest 1 mm	Changes from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Blood pressure	Automatic sphygmomanometer, average of two seated readings	Change from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Fat mass/fat-free mass	Dual-energy X-ray absorptiometry	Change from week 0 to 15, 30, & 56	Mean	Weeks 0, 30 & 56
Energy expenditure and energy intake				
Resting energy expenditure	Indirect calorimetry, average of 10 stable minutes of measurement	Change from week 0 to 30	Mean	Weeks 0 & 30
Total daily energy expenditure	Doubly labeled water method, average total daily energy expenditure over a 14-day period	Changes from week 0 to 30	Mean	Weeks 0 & 30
Energy intake	Doubly labeled water method, % caloric restriction over the interval between dual-energy X-ray absorptiometry measurement	Mean over week 0 to 30	Mean	Weeks 0 & 30
Non-exercise PA & sedentary behavior				
Non-exercise PA	ActivPAL™ thigh-worn activity monitor 14-day measurement, light physical activity (1.5 to < 3.0 METs), moderate-to-vigorous physical activity (≥ 3.0 METs)	Changes in light and moderate-to-vigorous PA from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Sedentary behavior	ActivPAL™ thigh-worn activity monitor 14-day measurement, sitting/lying (< 1.5 METs)	Change in sedentary time from week 0 to 15, 30, and 56	Mean	Weeks 0, 15, 30, & 56
Food cravings & eating behavior				
Food cravings	Food Craving Inventory [29]	Change from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Eating behavior	Food Preference Questionnaire Trait, reduced [30], Three-Factor Eating Questionnaire [31], Behavioral Risk Factor Surveillance System Alcohol Consumption Questionnaire [32], Binge Easting Scale [33], early eating away from home [34], early sugar-sweetened beverage consumption [34], modified Yale Food Addiction Scale [35], Palatable Eating Motives Scale [36], reward-based eating drive [37], Eating Behavior Inventory [38]	Change from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Meal timing & macronutrient intake				
Meal timing	Photo-based food diary	Change in meal timing parameters from week 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56

Table 2 (continued)

Domain	Specific measurement	Specific metric	Method of aggregation	Time-point
Macronutrient intake	Photo-based food diary	Change in macronutrient intake from baseline to weeks 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Sleep				
Objective measures of sleep duration, efficiency, timing, and regularity	Wrist-worn Actiwatch-2 + sleep diary 14-day measures	Change from weeks 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Subjective sleep quality and sleep-related daytime functioning	Pittsburg Sleep Quality Index [39], Epworth Sleepiness Scale [40]	Change from weeks 0 to 15, 30, & 56	Mean	Weeks 0, 15, 30, & 56
Cardiorespiratory fitness & exercise energy expenditure				
Cardiorespiratory fitness	Maximal aerobic capacity (VO2 max) from graded treadmill test	Change from week 0 to 30 & 56	Mean	Weeks 0, 30, & 56
Other				
Metabolic/hormonal evaluations	Serum lipid panel, glucose, insulin, and hemoglobin A1c	Change from week 0 to 30 & 56	Mean	Weeks 0, 30, & 56
Psychosocial, behavioral, and environmental predictors of adherence	Morning-Eveningness Questionnaire [41], Munich Chronotype Questionnaire [42], Physical Activity Enjoyment Scale [43], Barriers Self-Efficacy Scale [44], Behavioral Regulations for Exercise Questionnaire [45], Perceived Stress Scale [46], Positive and Negative Affect Scale [47], RAND 36-Item Health Survey [48], Short Grit Scale [49], Marijuana Use [32], Compensatory Health Beliefs Scale [50], Social Support for Healthy Behaviors [51], Behavioral Based Identity [52], Life History [53], and Neighborhood Environment Walkability Scale [54]	Change from week 0 to 15, 30 & 56	Mean	Weeks 0, 15, 30, & 56

calculated as TDEE − REE − exercise EE − thermic effect of food (TEF, estimated at 10% of TDEE).

EI will be assessed using the DLW intake-balance method [58] using the TDEE measure (described above) combined with the change in body energy stores (ΔES) using the following equation: EI = TDEE + ΔES [59]. This method of assessing EI using DLW has been reported to be the most robust method to quantify free-living EI during a period of potential energy imbalance over longer periods of time [58]. Change in body energy stores will be calculated for both FM and FFM from the DXA. Changes in FM (g) and FFM (g) will be converted to ΔES (kcal/day) using the energy coefficient 9.3 kcal/g and 1.1 kcal/g, respectively [58]. Change in body energy stores (kcal/day) will also be calculated using regression of daily home weights around the 14-day DLW measure of TDEE using an energy coefficient of 7.4 kcal/g.

Non-exercise PA and sedentary behavior

Non-exercise physical activity, and sedentary time, will be measured using the activPAL™ thigh-worn activity monitor (activPAL4, PAL Technologies, Glasgow, Scotland) for 14 consecutive days at baseline and weeks 15, 30, and 56. A 14-day measurement is preferred; however, this may be shortened to 7 days in certain circumstances due to holidays or participant travel. The activPAL4 uses accelerometer-derived information about thigh position to estimate time in different body positions (i.e., sitting/lying, standing, and stepping). The device will be attached to the anterior part of the right thigh using medical-grade adhesive dressings and waterproofed by wrapping it in a nitrile sleeve. This allows for the device to be worn while showering and overnight for 24-h measurement of physical activity, including wake and sleep behavior.

The raw activPAL.datx files will be processed using PALBatch software using the CREA 24-h wear protocol (allows for 4 h of non-wear per day) and autocorrecting for inverted wear (PAL Technologies Ltd., 2024). The ActivPAL will estimate time spent engaging in light physical activity (1.5 to < 3.0 METs), moderate-to-vigorous physical activity (≥ 3.0 METs), and sitting/lying (sedentary behavior, < 1.5 METs) [60, 61]. Participants will also be asked to record all exercise and bed and wake times in a log during the wear period. Non-exercise PA will be calculated as time spent engaging in activity ≥ 1.5 METs outside of exercise sessions—exercise session data will be manually excluded. It is anticipated that some participants will have reduced wear time due to scheduling constraints, skin sensitivity, or other device-related issues. Data will be considered valid for participants with ≥ 3 weekdays and ≥ 1 weekend day of wear. A valid day will be operationalized as ≥ 20 h of wear time over a 24-h period.

Food cravings and eating behavior

To assess compensatory eating behavior in response to the exercise intervention, validated questionnaires will be used to examine food cravings and aspects of eating behavior at baseline and weeks 15, 30, and 56. Questionnaires were chosen based on constructs found to differ significantly between compensators and non-compensators in a prior exercise study [4]. Frequency of cravings for specific foods will be measured with the Food Craving Inventory (FCI-II) [29]; preferences for high fat/high carbohydrate foods will be measured with the Food Preference Questionnaire Trait, reduced (FPQ-T-r) [30]; and aspects of eating behavior will be measured with the Three-Factor Eating Questionnaire (TFEQ R-18) [31]. We will also use the BRFSS Alcohol Consumption Questionnaire [32], Binge Eating Scale (BES) [33], early eating away from home [34], early sugar-sweetened beverage consumption [34], modified Yale Food Addiction Scale [35], Palatable Eating Motives Scale (PEMS) [36], reward-based eating drive (RED) [37], and the Eating Behavior Inventory (EBI) [38] to assess changes in eating behavior.

Meal timing, dietary macronutrient intake, and visual analog scale (VAS) measures

Meal-timing patterns (24 h) will be assessed using a photo-based food diary over three consecutive days (two weekdays, one weekend day) at baseline and weeks 15, 30, and 56. Participants will use a smartphone camera to take a picture of any food or drinks they ingest and send the photos (along with brief descriptions) via text message to the TIMEX Study's Google Voice account. To ensure consistency and quality of the photographs, participants will be given detailed instructions and asked to send before and after consumption pictures—allowing for timestamps of when meals were consumed. Dietary macronutrient intake will be quantified from the 3-day photographic food records [62] by the Colorado Clinical Translational Research Institute (CCTSI) Nutrition Core using Nutrition Data System for Research software. Additionally, calculations of the daily eating window duration (time of last intake—time of first intake) and midpoint of the eating window (clock time between first and last intake events) will be calculated for each assessment timepoint.

Over the same 3 days as the photo-based food diary, participants will receive text messages with a link to a REDCap survey every 2 h between 6 a.m. and 10 p.m. The surveys consist of visual analog scales (VAS) to assess hunger, satiety, sleepiness, energy/vigor, and fatigue. Study staff will be able to see participant responses in real time via the web-based interface to ensure VAS are completed at appropriate times and send reminders, if

necessary. The study team is experienced in this methodology [16].

Sleep

Sleep duration and timing will be estimated using the wrist-worn Actiwatch-2 (Philips Respironics, Murrysville, PA, USA) at baseline and at weeks 15, 30, and 56. Participants will wear the device 24 h/day for 14 consecutive days. A 14-day measurement is preferred; however, this may be shortened to 7 days in certain circumstances due to holidays or participant travel. Additionally, participants will be asked to keep a sleep diary over the assessment period, which includes bedtime, waketime, daytime naps, and a rating of each night's sleep quality. Wrist actigraphy yields relatively accurate and precise measures of sleep duration and timing compared to polysomnography [63, 64]. Sleep data will be scored using standardized methodology [65]. Established subjective measures of sleep quality and sleepiness will also be captured via questionnaire using the Pittsburgh Sleep Quality Index (PSQI) [39] and Epworth Sleepiness Scale (ESS) [40].

Cardiorespiratory fitness testing via maximal aerobic capacity (VO_2 max)

To assess cardiorespiratory fitness, maximal aerobic capacity (VO_2 max) will be measured at baseline, week 30, and week 56. During a 5-min warm-up, treadmill speed will be adjusted to elicit a HR that is approximately 70% of the age-predicted maximum HR. This speed will be maintained through the test, and the grade will be increased by 2% every 2 min until volitional exhaustion or until the test is stopped by the proctor.

Oxygen and CO_2 content of expired air will be measured continuously by open-circuit spirometry and averaged every 20 s using an automated online system (TrueMax 2400; Parvo-Medics, Sandy, UT, USA). Maximal oxygen consumption (VO_2 max) will be the highest average of two consecutive 20-s intervals. Evidence that VO_2 max has been attained will include reaching at least two of the following: a plateau in VO_2 despite an increase in exercise intensity, a respiratory exchange ratio > 1.10, and a HR max within 10 beats of the age-predicted value. Affective response to exercise will be measured with the Feeling Scale (FS), a one-item measure of affective valence ranging from 5 (I feel very good) to − 5 (I feel very bad) immediately pre, at each stage of the test, immediately post, 5 min post, and 10 min post these tests.

Exercise energy expenditure (EE) and exercise prescription adjustment

Exercise EE will be tested four times per participant during the 30-week supervised exercise program. The test will utilize a patient-specific protocol—each participant will start by walking or jogging on the treadmill at a speed and grade that elicits a heart rate that matches the prescribed heart rate for their exercise training sessions (prescriptions will begin at 70% of HRmax and progress to 80% of HRmax). Heart rate maximum will be defined individually as the maximum heart rate reached during the participant's baseline VO_2 max assessment. Heart rate will be monitored continuously with the Polar H10 HR monitor.

The objective of the test is for each participant to exercise for 30 consecutive minutes at their target HR (± 5 BPM) by adjusting the treadmill speed/grade accordingly. During the test, the participants' breath will be collected via a mouthpiece/facemask system and indirect calorimetry (Parvo Medics TrueOne 2400, Salt Lake City, UT, USA) providing information about the amount of energy expenditure during exercise, which will be used to determine exercise prescription durations to achieve the target kcal per week exercise EE for each participant. For example, if a person expends 10 kcal/min at 75% HRmax, then they will need to exercise for 50 min per session (10 kcal/min × 50 min = 500 kcal). Exercise prescriptions will be adjusted accordingly after each test.

Metabolic/hormonal evaluations

Serum lipid panel, glucose, insulin, and hemoglobin A1c will be measured after an overnight (12 h) fast at baseline and at weeks 30 and 56 and analyzed by the CU AMC CTRC Core Laboratory. Blood will be stored for assessment of additional markers of metabolic health (including markers of inflammation, lipid metabolism, thyroid hormones and metabolites, cortisol and other stress response hormones, gut metabolites, and hunger/satiety hormones).

Psychosocial, behavioral, and environmental predictors of exercise intervention adherence and response

To assess and measure psychological, social, behavioral, and environmental dimensions that may predict, moderate, or mediate intervention adherence and response (weight loss and changes in other outcomes), participants will complete several validated surveys and questionnaires at baseline and then again at weeks 15, 30, and 56—allowing the research team to determine if there are changes over time in any of the evaluated constructs. The selection of questionnaire measures was informed by the recommendations of the National Institutes of Health ADOPT Core Measures Project [66–68]. These questionnaires include the following: the Morning-Eveningness Questionnaire (MEQ) [41], Munich Chronotype Questionnaire (MCTQ) [42], Physical Activity Enjoyment Scale (PACES) [43], Barriers Self-Efficacy Scale (BARSE) [44], Behavioral Regulations for Exercise Questionnaire

(BREQ-3) [45], Perceived Stress Scale (PSS) [46], Positive and Negative Affect Scale (PANAS) [47], RAND 36-Item Health Survey [48], Short Grit Scale [49], marijuana use [32], Compensatory Health Beliefs Scale [50], social support for healthy behaviors [51], behavioral-based identity [52], life history [53], and Neighborhood Environment Walkability Scale (NEWS-A) [54].

Participant timeline {13}

See Table 3 for a detailed accounting of the participant timeline.

Sample size {14}

This trial is powered to detect a between-group difference (AM-Ex and PM-Ex) in change in weight (0–30 weeks) of 2.5 kg. A 2.5 kg between-group difference in weight loss was deemed the minimum difference of clinical importance [2], and 64 participants per arm (total study $N=128$) will be enrolled. The primary analysis will use the ITT principle in which all randomized participants are analyzed. Although specific data on the standard deviation (SD) of change in weight in response to the proposed intervention is unavailable, estimates of SD were obtained from MET-2 (common SD of 3.7 kg, 2000 kcal/week group) [15].

Assuming a common SD of 3.7 kg, a sample size of 64 per arm (total study $N=128$) would allow us to detect a clinically meaningful difference of 2.5 kg with 96% power at $\alpha=0.05$ level of significance. This is equivalent to a medium-large effect size ($d=0.67$) based on guidelines suggested by Cohen [69]. Because MET-2 used a per-protocol analysis, the SD of weight change may be larger in this ITT trial. Thus, we have conservatively designed the study to have 80% power for our primary ITT analysis if the SD were to be higher ($SD=5.0$, $d=0.50$). This range of SD in weight change from supervised exercise interventions is appropriate based upon previous studies of similar duration [4, 12]. Missing data will be fully recovered as discussed above which will remove or minimize (if present) confounding effects of missingness on our statistical power. With a combined attrition/failure to meet $\geq 75\%$ exercise adherence rate as high as 30%, we retain $\geq 80\%$ power in our sensitivity analyses (completers, per protocol) up to a common SD $=4.2$ ($d=6.0$) assuming the same threshold for clinical importance (2.5-kg difference in weight loss). Given the limited preliminary data, exact power calculations are not possible for our secondary outcomes. However, assuming a type I error rate of 5%, the minimal detectable effect size (MDES) for secondary outcomes was calculated. We are sufficiently powered at 80% to detect differences of 0.50 SDs or greater which is considered a medium MDES [69].

Recruitment {15}

Potential participants will be recruited from CU AMC and the surrounding Metro Denver Area through mass emails, flyers, social media advertising (Facebook, Instagram, etc.), and the CU School of Medicine research website (which maintains an updated list of available studies performed on campus that is also accessible to the general population). All advertisements will include a link to a study landing page on which more details about the study will be provided, including a description of the study requirements and eligibility criteria.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization sequence will be generated by the study biostatistician (E. W.). Using a computer-generated randomization sequence, participants will be stratified by sex and randomized within strata in a 1:1 ratio to AM-Ex and PM-Ex with equal probability using variably sized permuted block randomization.

Block randomization will be used to ensure approximately equal accrual to each arm from each stratum over time.

Concealment mechanism {16b}

Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from past assignments. Treatment allocation will take place after eligible participants have completed all baseline assessments, based on an a priori randomization list generated by the study biostatistician.

Implementation {16c}

The study biostatistician will be responsible for generating the allocation sequence. The assignment sequence (e.g., randomization list) is concealed from all study staff and investigators except the study biostatistician. Prior to the intervention start date, the study coordinator provides the biostatistician with a list of eligible participants who have completed all screening procedures and baseline measures. This list includes only participant ID's and their sex assigned at birth. Following a predetermined randomization sequence, each participant will be randomly assigned to their study condition. The biostatistician will then email the study coordinator a list detailing each participant's condition assignment ~ 24 h in advance of the intervention start date for the cohort. Participants are informed of their randomized study condition during the orientation

Table 3 Schedule of enrollment, interventions, and assessments for the TIMEX study participants

	Enrollment	Baseline and Allocation	Post-allocation Supervised Exercise Program						Close-out Unsupervised Exercise Program
TIMEPOINT*	$-t_1$ Weeks (-25) - (-5)	0 Weeks (-5) - 0	t_1 Week 3	t_2 Week 9	t_3 Week 15	t_4 Week 17	t_5 Week 23	t_6 Week 30	t_7 Week 56
ENROLMENT:									
Eligibility screen**	X								
Informed consent	X								
Screening Questionnaires	X								
Screening Labs	X								
EKG	X								
History + Physical Exam	X								
Allocation		X							
INTERVENTIONS:									
Morning Exercise (AM-Ex)			◆	—	—	—	—	—	◆
Evening Exercise (PM-Ex)			◆	—	—	—	—	—	◆
ASSESSMENTS:									
Bodyweight#	X	X			X			X	X
Body Composition (DXA)		X						X	X
Height	X								
Blood Pressure	X	X			X			X	X
Waist Circumference		X			X			X	X
Stored Blood for Future Use		X			X			X	X
Outcome Labs##		X						X	
VO_2 Max		X						X	X
Exercise EE			X	X		X	X		
REE		X						X	
TDEE & EI		X						X	
Device Measured MVPA, Sedentary Time, & Sleep		X			X			X	X
Self-reported EI & Macronutrient Intake		X			X			X	X
Stool Sample Collection		X			X			X	X
Metabolic/Hormonal Evaluations		X			X			X	X
Psychosocial, Behavioral, Environmental Constructs, & Other Questionnaires###		X			X			X	X

Table 3 (continued)

EKG electrocardiogram, *DXA* dual-energy X-ray absorptiometry, VO_2 *max* maximal oxygen consumption, *EE* energy expenditure, *REE* resting energy expenditure, *TDEE* free living total daily energy expenditure, *EI* energy intake, *MVPA* moderate to vigorous physical activity

[*] All measures, post-allocation, will occur ±2 weeks from when the measure is due

[**] Screening measures include weight, height, blood pressure, blood tests (comprehensive metabolic panel, lipid panel, complete blood count, thyroid-stimulating hormone, hemoglobin A1C, and pregnancy test in women of childbearing potential), the Beck Depression Inventory (BDI), the Eating Attitudes Test (EATS-26), the Questionnaire on Eating and Weight Patterns-5 (QEWP-5), and the Physical Activity Readiness Questionnaire Plus (PAR-Q+)

[#] Body weight measured in the morning after an overnight fast using a digital scale accurate to ±0.1 kg at baseline and weeks 15, 30, and 56. Participants will also be given a smart scale for daily home weighing. Weights will be transmitted via wireless cellular network to a secure website

[##] Outcome labs include fasting glucose, insulin, lipids, and hemoglobin A1c

[###] Questionnaires include Physical Activity Enjoyment Scale (PACES), Behavioral Regulations for Exercise Questionnaire (BREQ-3), Barriers Self-Efficacy Scale (BARSE), Morningness-Eveningness Questionnaire (MEQ), Munich Chronotype Questionnaire, Compensatory Health Beliefs Scale, Perceived Stress Scale (PSS), modified positive and negative affect schedule (PANAS), Exercise Benefits/Barriers Scale, POMS 40-item, behavior-based identity, BRFSS marijuana use, Short Grit Scale, intervention preference questionnaire, life history questionnaire, Marijuana Use DFAQ Inventory, social support for healthy behaviors, Short Form Self-Regulation Questionnaire (SSRQ), RAND 36-Item Health Survey, Pittsburgh Sleep Quality Index (PSQI), NEWS-A, Food Craving Inventory (FCI-II), Food Preference Questionnaire Trait, reduced (FPQ-T-r), Three-Factor Eating Questionnaire (TFEQ R-18), BRFSS Alcohol Consumption Questionnaire, Binge Easting Scale (BES), early eating away from Home, early sugar-sweetened beverage consumption, modified Yale Food Addiction Scale, Palatable Eating Motives Scale (PEMS), reward-based eating drive (RED), and Eating Behavior Inventory (EBI)

session for the cohort, which occurs approximately 1 week prior to the exercise intervention start date.

Assignment of interventions: blinding

Who will be blinded {17a}

All investigators and study staff except for the study biostatistician (E. W.) will be blinded to the randomization scheme. All investigators and study staff will remain blinded to paired group assignment and outcome data until study completion (including completion of data analysis). Core laboratory staff performing outcome measures will be blinded to participant group assignment. It is not feasible to blind participants, study coordinators, and study staff supervising exercise to participant group assignment. However, participants will be blinded to the central hypothesis of the study (i.e., hypothesized superiority of AM-Ex vs PM-Ex for weight loss).

Procedure for unblinding if needed {17b}

NA. It is not feasible to blind participants to study group assignment.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Outcome measures will be conducted at the AHWC Clinical Research Center and the CU AMC CTRC by trained study staff. We will use standardized, study-specific data collection forms to record outcome values. The collection forms will be filed by timepoint into each participant's study binder. Anthropometric measures (e.g., height, weight, blood pressure) will be collected a minimum of two times, and the average value will be used for analysis. Questionnaires will be administered electronically to participants via email using REDCap and will be scored directly within REDCap via hidden, calculated fields.

Plans to promote participant retention and complete follow-up {18b}

We will ensure continuity of key staff supervising exercise over the study, so participants build relationships to provide inspiration and increase accountability. To enhance exercise adherence and promote retention, participants will engage in supervised exercise, receive biweekly adherence emails, complete a behavioral support curriculum, and receive small payments for completing exercise sessions. If adherence or retention is lower than expected, we will consider the following strategies applied to both groups: provision of additional behavioral support, widening AM/PM exercise windows, adding weekend exercise sessions, modest reduction in exercise volume, or other strategies suggested based on interviews with participants with low attendance or who drop from the study.

Data management {19}

All outcome data is transferred from the physical data collection forms to the study's REDCap database. Field range values are set to alert if a value is outside a specific range, and missing data will be tracked and checked. All data will then be site-verified by a second staff member, verifying the physical forms in each participant's binders to the electronic data entered on REDCap. Primary outcome data (weight) is double entered. A backup of the REDCap database is exported monthly to the secured study drive. Prior to any data analysis, the study biostatistician will generate reports of outcome data from the database and run descriptive statistics to look for outliers. In the presence of outliers, the original source documents and/or testing output will be checked for accuracy and to determine whether testing/sampling error indicates that the data should be excluded from analyses.

Confidentiality {27}

A participant identifier (ID) code for the data will be used such that data will not have the participant's name associated with it. The key linking participant name and participant ID code will be kept in a secured location, with only key personnel having direct access to the list. Participant ID codes will be used in all data entry and data analysis. The investigative team will be trained in accordance with both the Colorado Multiple Institutional Review Board (COMIRB) and the Health Insurance Portability and Accountability Act (HIPAA) compliance issues and will act to maintain confidentiality and protect health information. Electronic data will be stored on secure servers with a high level of security, controlled access, daily backup, and long-term retention of back-up files. Hard copies of study data will be kept in participants' charts in a locked, secured file cabinet in the PI's or study coordinator's office. Access to all study data will be restricted to the PI and research personnel.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood will be collected at baseline and at weeks 15, 30, and 56 and analyzed as above. Whole blood, serum, and plasma will also be processed and stored at − 80 °C for future ancillary studies. Stool samples will be self-collected by study participants at baseline and at weeks 15, 30, and 56 using a stool collection kit with detailed instructions. Participants will sterilely transfer ~ 1–2 g of stool to the provided collection tubes, store specimens at − 20 °C (home freezers), and transport them to the clinic on ice packs within a week of collection. Stool specimens will then be stored at − 80 °C until they are analyzed during future ancillary studies.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The efficacy of the intervention will be evaluated by comparing differences between the AM-Ex and PM-Ex groups in weight change (kg) at 30 weeks (primary endpoint, following supervised exercise program) and 56 weeks (secondary endpoint, following unsupervised exercise program). These analyses will be performed according to intent-to-treat (ITT) principles and followed by sensitivity analyses (e.g., completer's analysis, per-protocol analysis [participants with ≥ 75% adherence to supervised exercise]). Using maximum likelihood methods, we will use mixed model analyses with repeated measures to estimate weight change at 30 and 56 weeks and to test for statistical differences across groups in changes over time. Models will include random intercept, time, group, and group × time variables. A proper error covariance structure will be chosen based on model fit indicated by model likelihood, Akaike information criterion, and Bayesian information criterion. The results from the mixed models will be summarized with adjusted means and 95% confidence intervals (CI) by trial arm at each time point. Additionally, baseline variables including age, sex/gender, race/ethnicity, and BMI will be included as covariates in the linear mixed models to assess their potential moderating effect. Similarly, we will longitudinally compare the percentage of participants achieving 3% and 5% weight loss between groups at 30 and 56 weeks using generalized estimating equations.

Similar analyses as described above will be completed for each of the secondary and exploratory outcomes. Secondary outcomes will be presented with and without adjustments to account for multiple testing by controlling for the false discovery rate (10%) using the Benjamini–Hochberg procedure [70].

Additionally, we will use linear mixed models to explore the extent to which changes in other outcomes are associated with changes in weight, EI, and EE. Finally, we will explore the extent to which biologic, behavioral, psychosocial, and environmental variables moderate or mediate intervention response (e.g., changes in body weight, body composition, cardiometabolic outcomes, EI, EE, sleep, fitness, and eating/exercise behavior) within groups and in the cohort as a whole.

Interim analyses {21b}

NA. No interim analyses are planned for this study.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Although we are not powered for formal analysis, study results will be presented separately and in aggregate based on biological sex to enhance transparency and inform data interpretation.

Methods in analysis to handle protocol nonadherence and any statistical methods to handle missing data {20c}

Data analyses will be performed using SAS statistical software (Version 9.4, Cary, NC, USA). Baseline demographic and descriptive characteristics will be summarized globally, and by intervention group, using frequencies and percentages for categorical variables and means and SD (median [Q1, Q3] for non-symmetric data) for inherently quantitative variables. Prior to conducting analyses, we will audit the data for completeness and quality, including missing data. We will evaluate distributions to ensure that they meet assumptions of planned analyses, including the detection of outliers. Baseline demographics and primary outcomes will be

compared between participants with and without follow-up measures to inspect for potential bias. We will also assess whether data are missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR)—nonignorable. If variations in attrition might be explained by observed variables corresponding to the missing at random (MAR) assumption, then models will give valid inferences because they are likelihood based, and no special adjustments are necessary. If some of the variability in attrition might be explained by unobserved variables, we will consider imputing missing endpoint data using multiple imputation techniques [71] and will assess the sensitivity of our results to various assumptions of missing data patterns [72]. SAS procedures PROC MI and MIANALYZE will be used.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

This paper represents our complete protocol. Upon publication of results, individuals interested in obtaining underlying participant-level data and/or statistical code may contact the PI (V. C.) for more information.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

This single-site randomized trial does not have a coordinating center or trial steering committee. The trial will be supervised by the PI (V. C.) with input from study coinvestigators. Additional oversight will be provided by an independent safety officer who will review study conduct and progress on an annual basis as outlined in our NIH-approved Data and Safety Monitoring Plan (DSMP). Three senior-level professional research assistants (PRAs) supervised by the PI, will provide day-to-day organizational support for the trial including participant recruitment and obtaining informed consent and will oversee other study staff (PRAs and/or student workers) in scheduling and performance of outcome measures and data entry. The screening medical history and physical exams will be performed by the PI (V. C., a MD) or by a postdoctoral fellow (R. R., a DO), both of whom possess current board certification in endocrinology. The PI and the study PRAs will meet weekly to discuss trial conduct and progress including recruitment and retention. Coinvestigator meetings will be held monthly during the study startup phase and then as needed to discuss any issues that arise with trial conduct.

Composition of the data monitoring committee and its role and reporting structure {21a}

The intervention and measurement protocols pose minimal risk to participants. Because of this low-risk status, the data safety monitoring plan for this trial focuses on close monitoring by the PI (an MD with current board certification in endocrinology) in conjunction with an independent safety officer, along with prompt reporting of excessive adverse events and any serious adverse events to the NIH and to COMIRB. The safety officer will review the reports prepared by the study coordinator at the annual safety officer meeting and will determine whether there is any corrective action, trigger of an ad hoc review, or stopping rule violation that should be communicated to the study investigator, COMIRB, and the study sponsor.

Adverse event reporting and harms {22}

Adverse events will be collected non-systematically (i.e., we will capture any adverse events spontaneously reported by participants) and will be reviewed, collated, and evaluated by the PI within 72 h. All serious adverse events will be evaluated by the safety officer and the PI within 24 h. A summary table of adverse events (safety report) will be compiled on an ongoing basis and will be provided to the independent safety officer at the annual meeting. The summary table will include a description of the adverse event, the date of onset, severity, action taken, outcome, whether the adverse event was expected or unanticipated, and a determination of the relationship of the adverse event to study procedures. Adverse event reports and annual summaries will not include identifiable material, and participants will be identified only by study ID number.

Frequency and plans for auditing trial conduct {23}

To review study conduct throughout the trial period, study team meetings, led by the PI (V. C.), will occur on a weekly basis. The independent safety officer will review trial conduct and progress annually, as outlined in our NIH-approved Data and Safety Monitoring Plan (DSMP). An annual report will be submitted for continuing review per COMIRB requirements. Lastly, an annual progress report will be submitted to the study sponsor (NIH).

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants and ethical committees) {25}

Any protocol changes that impact study procedures or risk to human participants will be approved by COMIRB and reflected in a revised consent form that will be reviewed and signed by all active participants. Protocol changes will also be reported to NIH during the annual progress reports.

Dissemination plans {31a}

Findings from this study will be shared publicly and disseminated mainly by publication in peer-reviewed journals and conference presentations. Journal articles will be submitted to PubMed Central in compliance with NIH access guidelines. Main outcomes are planned to be submitted for publication during 2026–2027. Peer-reviewed findings will also be disseminated through CU AMC social media outlets.

Research data, which documents, supports, and validates research findings, will be made available after the main findings from the final research data set have been accepted for publication. No research data with personal identifiers will be published under this project.

Discussion

Previous observational and experimental studies suggest that exercise time of day may alter weight loss and energy balance regulation, yet only a few short-term (≤12 weeks) prospective studies have examined the effects of exercise timing on body weight or fat mass in adults with overweight or obesity. Alizadeh et al. [17] randomized women with a BMI of 25–30 kg/m^2 to 6 weeks of supervised morning or afternoon exercise of equivalent duration (90 min/week). This study was not powered to detect differences in weight change; however, in a completers analysis, body weight decreased more in morning exercisers compared to afternoon exercisers (−1.6 vs −0.3 kg, SD not reported, $p=0.04$). Self-reported EI also tended to decrease more in morning exercisers compared to afternoon exercisers (−362 vs −28 kcal/day, $p=0.06$). Similarly, Arciero et al. found that women who completed 12 weeks of multimodal exercise in the morning lost more fat mass (−1.0 ± 0.2 kg) compared to women who completed evening exercise (−0.3 ± 0.2 kg) [18]. No differences in fat mass loss were observed for men. In a pilot trial, we randomized men and women to 15 weeks of supervised aerobic exercise progressing to 2000 kcal/week. We found that morning exercisers lost −0.9 ± 2.8 kg and evening exercisers lost −1.4 ± 2.3 kg with no significant differences between groups [16]. Two recent trials also found that 12 weeks of morning and evening exercise resulted in no significant differences in weight loss [20, 21]. In contrast, Di Blasio et al. [23] reported results of a non-randomized study of postmenopausal women participating in a 12-week walking program; participants self-selected morning or evening walking (200 min/week). While change in body weight did not differ between groups, the evening group experienced a greater decrease in fat mass (−1.7 kg vs −0.2 kg, p=0.04). Similarly, Mancilla et al. recently found that evening exercise resulted in greater reductions in fat mass (−1.2 ± 1.3 kg) compared to morning exercise (−0.2 ± 1.0 kg) following 12 weeks of exercise training [22]. Thus, to date, the study of the effect of exercise time of day on weight and fat mass has shown variable results. However, it is important to note the limitations of these prior studies. The duration of the exercise interventions (≤12 weeks) is generally too short to produce clinically meaningful weight loss and limits the ability to draw conclusions about the potential magnitude of between-group differences in weight loss with longer interventions. In addition, objective measures of energy balance (EI and EE) were not included in these studies; thus, compensatory mechanisms in response to morning versus evening exercise remain unknown. Additional limitations of these studies include the following: nonrandomization, heterogenous samples, and varying exercise prescriptions that do not align with guidelines for weight loss. Given the substantial limitations of these prior studies, a recent review concluded there is a need for fully powered, randomized trials to clarify the effects of exercise timing on weight loss [73].

The TIMEX study will fill this important gap in the literature by comparing the weight loss effectiveness of a guidelines-based dose (progress to 2000 kcal/week) of moderate intensity aerobic exercise performed in either the morning or the evening over a 30-week supervised exercise phase and a subsequent 26-week unsupervised exercise phase. We will use objective methods to measure EE (DLW), EI (DLW intake balance method), and PA (activPAL device) to allow for an accurate comparison of the impact of morning versus evening aerobic exercise on compensatory changes in EI and EE. Our findings may have significant public health implications as this study will generate robust data regarding whether there is an optimal time of day to exercise to enhance weight loss response. While not a primary objective, this trial will also provide important information on whether there are differences in adherence to morning versus evening exercise. We anticipate that results will further our understanding of the impact of morning versus evening exercise on cardiometabolic risk parameters and energy compensation in response to exercise and will provide preliminary insight into the impact of consistent exercise timing on circadian cues known the impact body weight regulation.

Trial status

This study protocol was based on protocol version number 21–3094 date February 20, 2025. Enrollment began on 12/07/21 and is anticipated to be completed on 4/07/2025.

Abbreviations

AM-Ex	Morning exercise
PM-Ex	Evening exercise

EI	Energy intake
EE	Energy expenditure
PA	Physical activity
TDEE	Total daily energy expenditure
ITT	Intent to treat
CU AMC	University of Colorado Anschutz Medical Campus
AHWC	Anschutz Health and Wellness Center
CTRC	Clinical Translational Research Center
UCH	UCHealth University of Colorado Hospital
BMI	Body mass index
PI	Principal investigator
MD	Medical doctor
BDI	Beck Depression Inventory
EATS-26	Eating Attitudes Test
QEWP-5	Questionnaire on Eating and Weight Patterns-5
PAR-Q+	Physical Activity Readiness Questionnaire Plus
HR	Heart rate
MHR	Maximum heart rate
CHR	Constant heart rate
BMP	Beats per minute
ACSM	American College of Sports Medicine
FS	Feeling Scale
DPP	Diabetes Prevention Program
DXA	Dual-energy X-ray absorptiometry
WC	Waist circumference
NIH	National Institutes of Health
BP	Blood pressure
FM	Fat mass
FFM	Fat-free mass
REE	Resting energy expenditure
DLW	Doubly labeled water
APE	Atom percent excess
TEF	Thermic effect of food
ΔES	Change in body energy stores
FCI-II	Food Craving Inventory
FPQ-T-r	Food Preference Questionnaire Trait, reduced
TFEQ-R-18	Three-Factor Eating Questionnaire
BES	Binge Eating Scale
PEMS	Palatable Eating Motives Scale
RED	Reward-based eating drive
EBI	Eating Behavior Inventory
CCTSI	Colorado Clinical Translational Research Institute
VAS	Visual analog scale
PSQI	Pittsburg Sleep Quality Index
ESS	Epworth Sleepiness Scale
VO2 max	Maximal oxygen consumption
PRP	Platelet-rich plasma
ADP	Adenosine diphosphate
SD	Standard deviation
MDES	Minimal detectable effect size
ID	Participant identifier
COMIRB	Colorado Multiple Institutional Review Board
HIPPA	Health Insurance Portability and Accountability Act
CI	Confidence interval
MCAR	Missing completely at random
MAR	Missing at random
MNAR	Missing not at random
DSMP	Data and Safety Monitoring Plan
PRAs	Professional research assistants

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Authors' contributions {31b}
VC, SC, EW, JD, EM, and AC conceived of and designed the study and obtained funding. VC wrote the protocol and acquired the data. EW performed the power analysis. SC, KO, SP, LW, MB, KC, and VC drafted the manuscript. SP generated the tables. All authors were involved in writing and revising the manuscript and approved the final version of the manuscript.

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Data availability {29}
All data that will be used or analyzed in the study will be supplied upon reasonable request.

Declarations

Ethics approval and consent to participate {24}
The study protocol was approved by the Colorado Multiple Institutional Review Board of the University of Colorado (COMIRB, Aurora, CO, USA; protocol 21–3094). Written informed consent to participate will be obtained from all participants.

Consent for publication {32}
Informed consent materials are attached as supplementary materials.

Competing interests {28}
The authors declare that they have no competing interests.

Author details
[1]Department of Medicine, Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [2]Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA. [3]Center for Health Promotion and Disease Prevention, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [4]Division of Physical Activity and Weight Management, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, USA. [5]Department of Kinesiology, Recreation, and Sport Studies, University of Tennessee, Knoxville, Knoxville, TN, USA.

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