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Time-restricted eating to improve cardiometabolic health: The New York Time-Restricted EATing randomized clinical trial – Protocol overview

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Abstract

Re-aligning eating patterns with biological rhythm can reduce the burden of metabolic syndrome in older adults with overweight or obesity. Time-restricted eating (TRE) has been shown to result in weight loss and improved cardiometabolic health while being less challenging than counting calories. The New York Time-Restricted EATing study (NY-TREAT) is a two-arm, randomized clinical trial (RCT) that aims to examine the efficacy and sustainability of TRE (eating window ≤10 h/day) vs. a habitual prolonged eating window (HABIT, ≥14 h/day) in metabolically unhealthy midlife adults (50–75 years) with overweight or obesity and prediabetes or type 2 diabetes (T2D). Our primary hypothesis is that the TRE will result in greater weight loss compared to HABIT at 3 months. The efficacy of the TRE intervention on body weight, fat mass, energy expenditure, and glucose is tested at 3 months, and the sustainability of its effect is measured at 12 months, with ambulatory assessments of sleep and physical activity (ActiGraph), eating pattern (smartphone application), and interstitial glucose (continuous glucose monitoring). The RCT also includes state-of-the-art measurements of body fat (quantitative magnetic resonance),

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CRediT authorship contribution statement

Leinys S. Santos-Báez: Visualization, Writing – original draft. **Alison Garbarini:** Writing – review & editing. **Delaney Shaw:** Writing – review & editing. **Collin J. Popp:** Writing – review & editing. **Emily N. C. Manoogian:** Visualization, Writing – review & editing. **Satchidananda Panda:** Visualization, Writing – review & editing. **Blandine Laferrère:** Funding acquisition, Conceptualization, Methodology, Visualization, Supervision, Resources, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CJP is a Sports Nutrition Consultant for Renaissance Periodization, LLC.

Appendix A. Supplementary data

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total energy expenditure (doubly-labelled water), insulin secretion, insulin resistance, and glucose tolerance. Adherence to self-monitoring and reduced eating window are monitored remotely in real-time. This RCT will provide further insight into the effects of TRE on cardiometabolic health in individuals with high metabolic risk. Sixty-two participants will be enrolled, and with estimated 30% attrition, 42 participants will return at 12 months. This protocol describes the design, interventions, methods, and expected outcomes.

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IRB: AAAS7791.

Keywords

Glucose; Continuous glucose monitoring system; Meal timing; Time-restricted eating; Prediabetes; Diabetes; Doubly labelled water

1. Introduction

Weight loss with caloric restriction can prevent the progression of prediabetes to type 2 diabetes (T2D) if untreated [1] and decrease the risk of cardiovascular disease (CVD) [2–7]. However, because caloric restriction is difficult to sustain long-term, alternative lifestyle interventions have been proposed, including reducing the duration of the daily eating window, or time-restricted eating (TRE) [8–30].

The majority of adults in the United States have an eating window that exceeds 15 h/day [11,31,32], a pattern often associated with obesity [33–35]. The temporal aspect of meal intake is an important target to decrease CVD risk [36–39]. Studies in mice [9,10] and humans [11–30,33–35] demonstrated that TRE could result in increased sleep satisfaction [11], improved insulin sensitivity, and reduced inflammation and oxidative stress, independent of weight loss [16].

Despite these intriguing findings, previous TRE clinical trials have limitations: small scale and short duration [16,17], targeting healthy individuals [11–14] or only men [12–17,25,30], severe time restriction [11,16,29], no account of habitual temporal eating patterns [16,18–20], no monitoring of adherence [12,13,15,19–21,24,27,30], or lack of randomization [16,21,23,25,27], with questionable clinical translation. Results from these studies are inconsistent, with some showing metabolic benefits [17,18,21,23,25], while others do not [11,19,24,26,27]. Therefore, further exploration of TRE with more rigorous study design and accurate methods to measure health outcomes is warranted.

Mobile health interventions allow real-time monitoring of behavior in an ambulatory setting [40–44]. Our objective is to test the efficacy of a 10-h TRE intervention, compared to habitual prolonged eating window (>14 h, HABIT), on CVD risk in metabolically unhealthy adults.

Enrollment began in May 2021 and will end in the Spring of 2024 for study completion in 2025.

We hypothesize that TRE will result in greater loss of fat mass (FM) and body weight compared to HABIT, and that these effects will be mediated by a decrease in total daily energy intake (EI) (Fig. 1).

Secondary outcomes include glucose levels, glycemic variability (GV), insulin resistance (assessed by the Matsuda Index and HOMA-IR), blood pressure, sleep duration and quality, and inflammation markers [45].

2. Study design

2.1. Study participants

The study is approved by the Columbia University Institutional Review Board (IRB). Participants will be men and women with overweight or obesity and prediabetes or T2D, of any racial or ethnic groups, aged 50 to 75 years, who have a prolonged eating window of ≥14 h/day (Table 1).

2.2. Recruitment

Potential participants, identified through flyers and brochures, websites, social media, community centers, health care provider referrals, and/or electronic medical records, are screened over the phone for inclusion/exclusion criteria (Table 1). Detailed information about the study is provided via Zoom, phone, or email with a link to a short descriptive YouTube video [46].

Eligible participants are instructed remotely to download the study application (app) on their smartphone and attend a 10-min coaching session on how to use the app, i.e. how to self-monitor in real-time by taking photos and/or logging their daily meals, snacks, and beverages during the 2-week remote screening phase. At completion of the 2-week remote screening, individuals with a prolonged daily eating window (≥14 h) [11,31,32] and at least 70% adherence to logging [31] are eligible for enrollment and proceed to sign the informed consent form prior to remotely completing the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI-II) questionnaires [47].

Individuals with adequate scores in the BAI and BDI-II questionnaires (Supplemental Table 1) are scheduled for an in-person screening visit at the Clinical Research Center (CRC) for medical history, physical examination, and fasted blood tests, including glycated hemoglobin (HbA1c), blood count, metabolic panel, fasting glucose, creatinine, lipids, liver profile, and thyroid stimulating hormone.

2.3. Intervention and study phases

This is a one-to-one randomized controlled prospective trial of 12-month duration (Fig. 2) taking place at Columbia University Irving Medical Center. After completion of the screening, enrolled participants undergo a 2-week baseline assessment, prior to being randomized to TRE or HABIT. Participants randomized to HABIT follow their daily habitual eating window. Those randomized to TRE will reduce their daily eating duration to a self-selected 10-h window, beginning within three hours of wake-up time and ending at least three hours before bedtime. Participants randomized to TRE will continue to follow

their 10-h window for the duration of the study. At the end of months 3 and 12, a repeat 2-week assessment is done.

Subjects randomized to TRE have the option to gradually transition from their baseline eating window to their self-selected TRE window over the course of the first two weeks (Supplemental Document 1). TRE participants receive daily push notifications 1-h before the start and 1-h before the end of their eating window.

Participants remain on their habitual medications, metformin included, during the entire duration of the study. Any change and/or adjustment made by the participants' providers is recorded.

Transportation by car service is offered to ensure timely arrival to the CRC. In addition, participants receive compensation for their time and effort following completion of each study period. The compensation schedule is the same for both groups.

2.3.1. Two-week baseline assessment—After enrollment, fasted participants visit the CRC on Day-1 for measurements of weight, height, waist circumference, and body composition via quantitative magnetic resonance (QMR) (Fig. 3); participants receive of a weight-based dose of doubly labelled water (DLW) for ingestion, are fitted with the continuous glucose monitoring sensor (CGM, Abbott Freestyle Libre Pro, Abbott Park, IL, USA) and Actigraph-GT3X (ActiGraph LLC, Pensacola, FL, USA), and complete the following questionnaires: Insomnia Severity Index (ISI) [48], Pittsburgh Sleep Quality Index (PSQI) [49] to assess self-reported sleep quality, Morningness-Eveningness questionnaire [50] to determine daily sleep-wake habits, visual analog scales (VAS) [51] to rate appetite and hunger, Berlin Questionnaire [52] to identify sleep apnea, and International Physical Activity Questionnaire (IPAQ) [53] to assess typical weekly physical activity levels (Supplemental Table 1).

For the following 12 days, participants follow a free-living routine at home and return to the CRC on Day-13 for a repeat QMR, to provide urine samples, and to eat a controlled eucaloric diet (Supplemental Fig. 1a and b) calculated with the Mifflin-St. Jeor equation [54,55]. The macronutrient composition of the diet is: 56–59% carbohydrates, 14–17% protein, and 26–28% fat.

The timing of the meals and composition of the diet on Day-13 are controlled and identical for both groups, followed by a 10-h overnight fast at baseline to mimic their habitual short overnight fast, and a 14-h overnight fast at 3 months, prior to the oral glucose tolerance test (OGTT) the next day. Breakfast and lunch are administered under staff supervision. Dinner and an evening snack are provided to the participants in an isothermal bag with preparation instructions provided by the research nutritionist. Participants log all the provided meals using the myCircadianClock (mCC) app and return containers, which are inspected for completion of meals upon return.

On Day-14, fasted participants report to the CRC at 7:30 am for a 2-h OGTT. At the completion of the OGTT, sensors are collected, and participants are randomized to HABIT or TRE.

2.3.2. Initial intervention: 3-month phase—During the following 3 months, participants in both groups continue logging daily meals, snacks, and beverages on the mCC app. However, those randomized to TRE follow their personalized 10-h eating window, and those randomized to HABIT follow their habitual eating schedule. Baseline assessments are repeated at the end of 3 months.

2.3.3. Sustainability of the intervention: 9-month phase—Participants remain in their assigned TRE or HABIT group for the remainder of the study. During the 9-month phase they are only asked to use the mCC app for the first ten days of each month. At 12 months, participants return to the CRC for a final 2-week assessment with the mCC app, ASA24, actigraphy, and fasting blood draw, but without DLW, CGM, and OGTT. All enrolled participants are blinded to ActiGraph, QMR, DLW, and CGM data. HbA1c results are shared after baseline, 3-month, and 12-month assessments.

3. Methods

3.1. Anthropometric measurements

Weight and height are obtained in triplicate on calibrated instruments on Day-1 and Day-13 at baseline and 3 months, and on Day-1 at 12 months. Prior to these measurements, participants must void, remove garments and jewelry, and change into a hospital gown and slippers.

Body weight is measured to the nearest 0.1 kg (Ohaus Champ General Purpose Bench Scale, Ohaus Corp., Pine Brook, NJ, USA) and height to the nearest 1 mm using a stadiometer (Holtain Ltd., Crymych, UK). Waist circumference is measured at baseline, 3 months, and 12 months in triplicate; the study physician locates the lowest point of the costal margins on the mid-axillary lines and the highest point of the iliac crests and marks the midpoint with a washable marker, bilaterally. The abdominal circumference is measured by aligning the two marks using the Gulick II measurement tape (Country Technology, Inc., Gays Mills, WI); results are recorded to the nearest 0.1 cm.

3.2. Body composition

Quantitative magnetic resonance (QMR, EchoMRI 2020, Echo Medical Systems, Houston TX, USA) is a noninvasive measure of body FM and is standardized to detect at little as 50-g change in FM [56,57]. This system generates a low magnetic field at 0.0068 Tesla and employs magnetic resonance relaxation analysis for measuring live body composition in terms of fat tissue, lean tissue, total body water, and free water. QMR is performed under fasting condition in duplicate by a trained technologist on Day-1 and Day-13 at baseline and 3 months, and Day-1 at 12 months. Fat-free mass (FFM) is calculated by subtracting FM from body weight.

3.3. Energy expenditure

Doubly labelled water (DLW) is the gold-standard method to assess free-living total energy expenditure (TEE) [58]. On Day-1 of the 2-week assessment at baseline and 3 months, a urine specimen is collected prior to the participant drinking a weight-based dose of DLW

containing 1.8 g/kg of total body water (TBW) of 10APE ^{18}O labelled water and 0.12 g/kg TBW of 99.9 APE ^{2}H labelled water [58,59]. Three timed urine samples are obtained at 1, 3, and 4 h after administration of the DLW dose on Day-1. On Day-13, two additional urine samples are obtained at times matching the 3-h and 4-h post-dose samples collected on Day-1. TEE measures the differential rates of elimination of stable isotope tracers ^{2}H (deuterium) and ^{18}O. Stable isotopes in tap water vary across geographic locations [60], thus, participants are instructed to limit travel to <200 miles from the New York City area for 2 weeks prior to and during each 2-week ambulatory period.

For each 2-week period, EI is calculated from the sum of TEE and changes in FM and FFM, measured by QMR. This is computed from the regression (slope, grams per day) of calibrated body weight obtained on Day-1 and Day-13 and changes in FM and FFM [58,61]. Long-term changes in energy balance will be estimated using QMR and DLW data collected at baseline and 3 months.

3.4. Eating patterns

The mCC app was developed and validated to monitor the daily temporal pattern of caloric intake in free-living conditions, via time-stamped photos of meals and beverages in the JPEG format [11,62]. Participants are instructed to use the in-app camera to take a photo of all meals and beverages prior to consumption in real time. A text entry option is enabled if subjects are unable to obtain a photo. The meal images and text entries are transferred to a remote server immediately after data submission. These entries are thoroughly reviewed by two independent trained research staff and compared with the ASA24® dietary recalls and glucose excursions from CGM (Sections 4.6. and 4.8.).

The app automatically sends reminders one hour prior to the start and the end of the eating window for participants in TRE.

3.5. Adherence

Self-monitoring and tailored feedback using smartphone technology increase intervention adherence [11]. Logging adherence is defined as the number of days with at least 2 daily entries separated by a minimum of 5 h. Adherence to the eating window is defined as logging all eating occasions (EO) within the self-selected 10-h window (±15 min, for TRE). Research staff monitor log entries daily and send personalized push notifications biweekly for the three 2-week ambulatory assessments, and weekly in the 3- and 9-month phases, to reinforce logging and eating window adherence. Additional contact by email or phone can occur as needed. The research staff keeps track of all contacts with participants.

3.6. Dietary recall

The ASA24® is a web-based, self-administered diet recall to assess energy, macronutrient, and micronutrient intake [63]. On Day-1 of the baseline assessment, participants receive detailed instructions along with a practice session under staff supervision. All participants are asked to complete 24-h recalls on two non-consecutive weekdays and one weekend day during each of the three 2-week ambulatory assessments (baseline, 3 months, and 12 months) and during months 6 and 9, and receive reminders to complete the dietary recalls

from the research staff. Participants are asked to complete an additional recall if missing data are reported, there is implausibly low or high caloric intake, or there is a discrepancy of >500 kcal between the three recalls.

3.7. Physical activity and sleep

Participants wear the ActiGraph-GT3X on their non-dominant wrist during each 2-week assessment period to obtain non-invasive measures of sleep and physical activity [64] and complete a sleep log to record wake-up time and in-bed times (Supplemental Document 2) as a backup measure. Sleep data include in-bed time, sleep onset time, wake time, out-of-bed time, total sleep time, sleep onset latency, sleep efficiency, total minutes in bed, wake time after sleep onset, total awakenings after sleep onset, average time per awakening, movement index, fragmentation index, and sleep fragmentation index. Sleep quality, timing, and duration are also assessed with the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI), the Berlin Questionnaire, and the Morningness-Eveningness questionnaire, administered at baseline, 3 months, and 12 months.

Physical activity data by actigraphy include daily/hourly kcals, metabolic equivalent of task (METs), amount and percent of the time in sedentary, light, moderate, vigorous, and very vigorous activity. Subjective estimation of activity levels is also assessed by the IPAQ Questionnaire, administered at the beginning of each 2-week assessment period.

3.8. Continuous glucose monitoring (CGM)

The CGM sensor (Abbott Freestyle Libre) is worn on the back of the non-dominant arm during the 2-week assessment periods at baseline and 3 months; it does not require calibration by finger sticks [65]. CGM glucose data are downloaded from LibreView software [65]. The EasyGV 8.6 software [66] is used to calculate mean amplitude of glycemic excursions (MAGE), which is the mean of blood glucose values, ignoring excursions of 1 standard deviation (SD) or less, and the largest amplitude of glycemic excursion (LAGE), which is the difference between the maximum and minimum blood sugar levels of a day.

3.9. Oral glucose tolerance test (OGTT)

To assess glucose tolerance and β-cell function, participants undergo a 2-h 75 g OGTT on Day-14 at baseline and 3 months. Participants on metformin remain on their medication for the duration of the ambulatory testing period. On the morning of Day-14, an intravenous catheter is inserted in an antecubital vein by a research nurse. Blood samples at –15 and 0 min are obtained immediately before 75 g glucose drink at 8:00 am, and again at 15, 30, 60, 90, and 120 min after the drink, before being centrifuged, aliquoted, and stored at −80C.

3.10. Visual analog scales (VAS)

At baseline and 3 months, sleep satisfaction, energy level, hunger, desire to eat, craving and fullness rating, and gastrointestinal symptoms are assessed by a 150 mm VAS before each meal and snack, and after each meal on Day-13; the same VAS are repeated under fasting condition on Day-1 at baseline, 3 months, and 12 months (Supplemental Document 3). VAS are anchored at each extremity with ‘not at all’ to ‘extremely’. A survey is administered on

Day-1 at 3 and 12 months to assess participants' acceptance of TRE, difficulty using the study app or adhering to intervention, and willingness to pursue TRE after study completion.

3.11. Biomarker assays

Biomarkers will be assessed at the Columbia Biomarker Core Laboratory and include: fasting blood glucose, HbA1C, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, β-hydroxylbutyrate, glycerol, free fatty acids, insulin, C-peptide, leptin, adiponectin, high sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α, total Receptor for Advanced Glycation End products, and 8-Isoprostane (Methods for biomarker assays are provided in Supplemental Table 2).

3.12. Statistical analyses

Primary and secondary outcomes are shown in Supplemental Table 3.

Randomization.—Individuals (n = 62) will be randomized to TRE or HABIT in a 1:1 ratio, stratified by overweight/obesity, gender (men or women), and age (≤60 or > 60). Permuted blocks with a block size of 2 will be used for the stratified randomization using the Microsoft Structured Query Language Server (MS-SQL) database, version T-SQL, to house the study data; random selection is performed using the T-SQL internal random number generator, using the current time as a seed.

Sample size justification.—The study is powered for the primary outcome: change in body weight. Based on our pilot study [11], assuming a standard deviation of 3.39 in each group, with 26 subjects per group, we will have 93% power to detect a weight difference of 3.27 kg weight loss between TRE and HABIT. The Type I error rate was controlled at 0.05. Based on our pilot study [31], we estimated that approximately 500 individuals need to be phone screened, 200 will enter remote screening, 130 will complete the remote screening, of which 60% will have a prolonged eating window. Assuming an estimated attrition rate of 30% over the 12-month intervention, 62 participants will be enrolled with the goal of retaining 52 participants at 3 months and 42 participants at 12 months.

Calculations.—We will calculate total under the curve (tAUC) and incremental under the curve (iAUC) area with the trapezoid method for glucose, insulin, and C-peptide [67]; the β insulinogenic index [II_{30min} = 0.007 x $insulin_{30min}$ (pmol/L) – $insulin_{0min}$ (pmol/L)]; insulin secretion rate by C-peptide deconvolution using a two-compartment model [68]; insulin resistance by the Matsuda Index, calculated as: 10,000/([fasting insulin (mU/mL) x fasting glucose (mmol/L)] x [mean OGTT insulin (mU/mL) x mean OGTT glucose (mmol/ L)]), and HOMA-IR, calculated as [fasting insulin (mU/ mL) x fasting glucose (mmol/L)]/22.5 [69–71].

Data analysis plans.—The treatment effect will be assessed using a linear mixed-effects model with weight as the outcome variable, treatment group (TRE, HABIT), and time (baseline, 3 months, 12 months) as main predictors, and a treatment-by-time interaction. The random effect is included in the model to account for within-subject correlation. A significant treatment-by-time interaction confirms the hypothesis. Treatment effect on other

outcomes will be analyzed similarly. To assess how the treatment affects change in body weight or FM from 0 to 3 months and from 0 to 12 months, a linear mixed model with change of FM (or body weight) from baseline as the outcome with similar analyses will be used.

The Preacher and Hayes' Bootstrap Method will be used to assess the mediating effect of EI and sleep duration on insulin resistance. Specifically, we consider linear models:

HOMA-IR change = $\beta 0 + \beta 1 * E$ intake change$+\beta 2 *$Group$+\varepsilon$;

EI change = $\Upsilon 0 + \Upsilon 1 *$Group$+\varepsilon$ HOMA-IR change = $\beta 0 + \beta 1 *$Sleep duration change$+\beta 2 *$Group$+\varepsilon$;

Change in sleep duration = $\Upsilon 0 + \Upsilon 1 *$Group$+\varepsilon$; where Group = 0 if assigned to HABIT and Group = 1 if assigned to TRE. The hypothesis H0: $\beta 1 * \Upsilon 1 = 0$ will be tested by the bootstrap method.

The treatment effect on glucose metabolism will be assessed formally using a linear mixed-effects model with either glucose tAUC or iAUC as the outcome variable, treatment group (1 = TRE, 0 = HABIT), and time (0 = baseline, 1 = 3 months, 2 = 12 months) as main predictors and a treatment-by-time interaction. The random effect is included in the model to account for within-subject correlation. A significant treatment-by-time interaction confirms the hypothesis.

Adherence will be calculated as the number and percentage of days meeting definition of logging adherence, and, for the TRE group, number of days meeting the target eating window and mean reduction of the duration of the eating window.

Various repeated measure linear models will be run to test the association of adherence on weight loss (and FM loss) at 3 and 12 months. Analysis will begin with a linear mixed-effects model with treatment, time, and their interaction, and then move on by controlling for the stratifying variables and baseline variables. These controlling variables will be dropped if not significant.

Handling of missing data.—To take full advantage of the strengths of the randomized design, it is necessary to maintain the full sample size in both intervention arms (TRE and HABIT). This will allow to adhere to the intention-to-treat principle. Missing data from dropouts will be handled using multiple imputation [72]. For the secondary completers-only, linear mixed models will be used, which do not require balanced groups at random assumption.

4. Adverse events

There are minimal risks associated with the intervention and sensor use, and subjects are made aware of any of the following potential risks before consent: the ActiGraph can cause mild skin irritation from the wrist strap; CGM could cause skin irritation, pain or discomfort, bruising, scarring, allergic reactions to the sensor, local infection, sensor breakage with

fragments retained under the skin; participants may experience claustrophobia during the QMR; the IV catheter insertion for the OGTT can result in bruising, inflammation, or infection.

The study staff ensures that potential participants understand these risks before enrollment and are given instructions to communicate with the study staff if any adverse event occurs, for immediate assessment by the study physician and sensor, assessment, or intervention discontinuation, as applicable.

5. Study limitations and potential pitfalls

Older individuals may not be able to navigate the smartphone app easily, but the screening process helps select individuals able to effectively operate the app. In an attempt to minimize study burden, the study design includes three 2-week ambulatory assessments and two half-day metabolic studies, and the TRE intervention is delivered primarily via the smartphone app. Monetary compensation is implemented to enhance retention. Should drop-outs be higher than expected, recruitment will continue to ensure 26 subjects per group at 3-month completion.

Some participants may find the TRE intervention difficult. Frequent contact after randomization and reassessment for goal setting specific to the timing of the eating window will be prioritized, within the limits defined by the protocol. Prior evidence suggests a 10-h eating window is feasible [31]. While duration of the eating window and overnight fast is fully controlled in the TRE group, participants self-select their eating window, which should increase compliance. Prior to the OGTT, the overnight fast is controlled and identical in both groups, with a fasting duration of 10 h at baseline and 14 h at 3 months, to obtain between-group consistency before testing glucose tolerance the following morning, and avoid overestimating any improvements in insulin sensitivity [16].

Physical activity is an important component of energy balance and fitness, which are predictors of weight maintenance after weight loss. Although selected participants are expected to be relatively sedentary, and it is unlikely that participants will increase their physical activity levels in response to the intervention, physical activity changes could be a confounder. Physical activity is measured and added as a covariate in the analysis.

The mCC app is available only in the English language and outcomes may not be generalizable to non-English speaking communities.

Dietary recall often results in underestimation of intake [73,74]. To limit this issue, recalls are completed on 3 non-consecutive days, following a thorough supervised ASA24 recall on Day-1 of the ambulatory assessment period.

Due to the nature of the behavioral intervention, participants and study staff are not blinded to randomization assignment, however, participants are blinded to body sensors data. Research staff obtaining anthropometries, QMR, and DLW, laboratory technicians, and statistician are blinded to group assignment.

6. Future studies

In-depth modeling of functional data of sleep, physical activity, meal pattern, and CGM-glucose could be done in future analyses and used to generate a predictive model of glucose control based on diet composition and meal timing. Blood samples will be stored for future metabolomics and proteomics analyses, including bile acids, a metabolic biomarker particularly affected by the fasting/feeding cycle. Future TRE interventions could target patients with other types of chronic conditions such as gastroesophageal reflux, younger individuals, and other ethnic groups, and/or implement TRE via eHealth in a clinical setting.

7. Conclusions

Calorie restriction, the recommended first approach to treat obesity and associated CVD, is resource-intensive to implement and difficult to sustain over time. TRE offers a potentially low-cost and sustainable approach to treating obesity. Daily energy intake is restricted within a consistent interval of 8 to 10 h, usually without explicitly attempting to modify diet composition or reduce calories. The rationale for TRE is based on the role of circadian rhythms in metabolism, as chronic circadian rhythm disruption increases the risk of obesity and metabolic diseases, hence, restricting the eating window sustains circadian rhythms and improves metabolism.

Past TRE trials have had mixed results, perhaps due to confounding effects of study design and subject selection. The NY-TREAT randomized trial provides an innovative approach by targeting metabolically unhealthy individuals with measured prolonged baseline eating windows and assessing their energy expenditure and body composition using state-of-the-art, highly precise methods. Therefore, this trial will clarify the role of TRE on energy balance in individuals with overweight and obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

No data was used for the research described in the article.

Abbreviations:

ALT	Alanine Transaminase
ASA24®	Automated Self-Administered 24-h Dietary Assessment Tool

AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAI	Beck Anxiety Inventory
BDI	Beck's Depression Inventory
BMP	Basic Metabolic Panel
CGM	Continuous Glucose Monitoring
CPAP	Continuous Positive Airway Pressure
CRC	Clinical Research Center
CVD	Cardiovascular Disease
DLW	Doubly Labelled Water
EDTA	Ethylenediaminetetraacetic Acid
EI	Energy Intake
EE	Energy Expenditure
ES	Energy Stores
eGFR	Estimated Glomerular Filtration Rate
EMR	Electronic Medical Records
FG	Fasting Glucose
FM	Fat Mass
FFM	Fat-Free Mass
HABIT	Habitual Eating
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
hsCRP	High Sensitivity C-Reactive Protein
IPAQ	International Physical Activity Questionnaire
ISI	Insomnia Severity Index
ITT	Intention-To-Treat
LDL	Low-Density Lipoprotein
mCC	myCircadianClock

MRI	Magnetic Resonance Imaging
MVPA	Moderate-to-Vigorous Physical Activity
NIA	National Institute on Aging
NHLBI	National Heart, Lung, and Blood Institute
NIA	National Institute of Aging
NCATS	National Center for Advancing Translational Sciences
OGTT	Oral Glucose Tolerance Test
OSA	Obstructive Sleep Apnea
PSQI	Pittsburgh Sleep Quality Index
QMR	Quantitative Magnetic Resonance
RAGE	Receptor for Advanced Glycation End Product
T2D	Type 2 Diabetes
TEE	Total Energy Expenditure
TG	Triglycerides
TNF	Tumor Necrosis Factor
TRE	Time-Restricted Eating
TSH	Thyroid Stimulating Hormone
VAS	Visual Analog Scales

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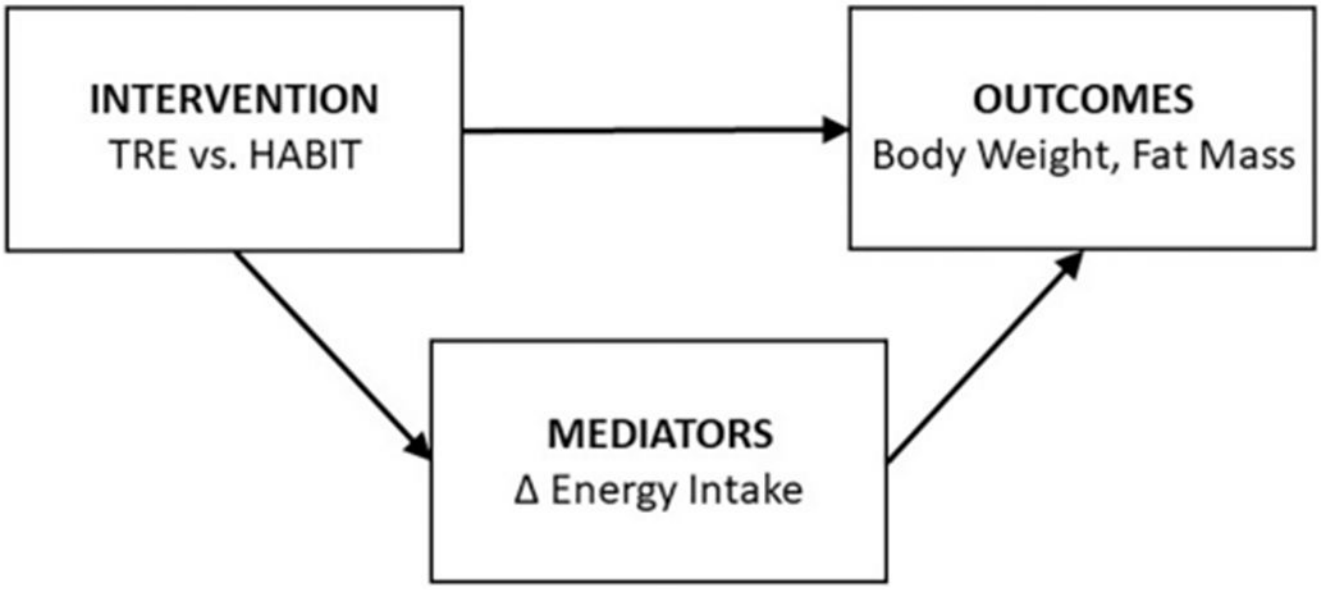

Fig. 1.
Working model.
The effect of TRE on fat mass and glucose will be mediated by decreased energy intake - assessed by doubly labelled water.

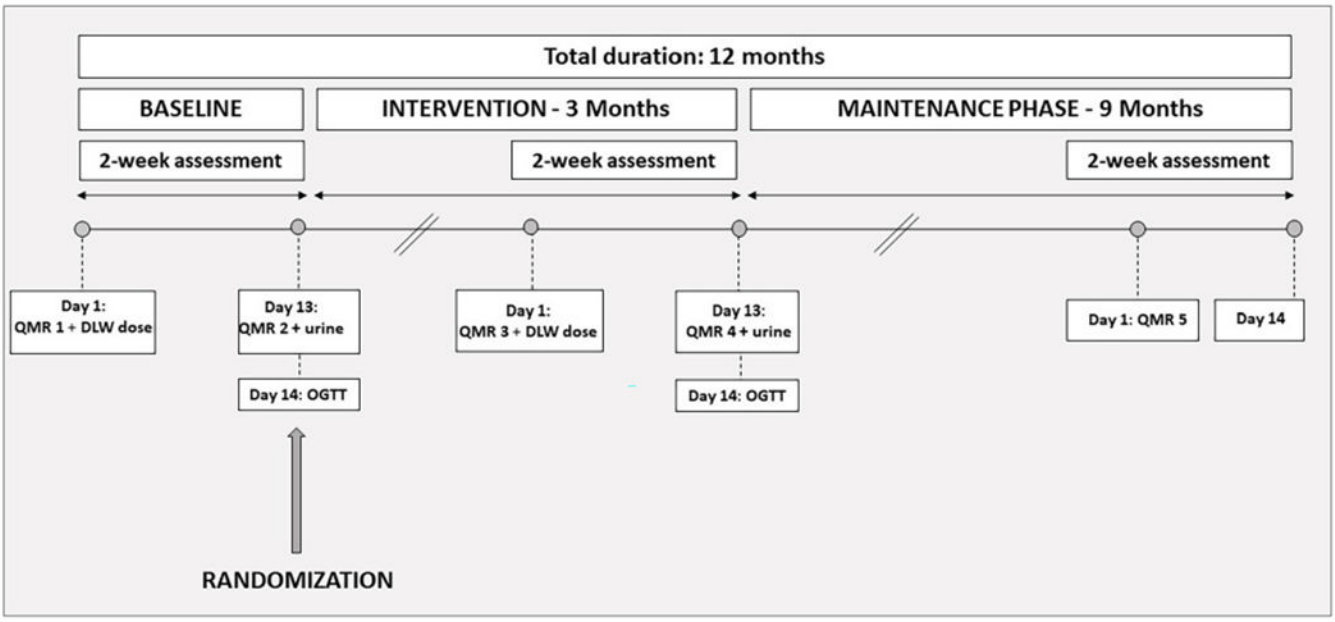

Fig. 2.

Study timeline.

After screening, participants are enrolled for a total duration of 12 months. They complete a baseline period of two weeks before randomization. Upon randomization, subjects enter the 12-month intervention, with a repeat 2-week assessment at the end of 3 months, and at 12 months. DLW = Doubly Labelled Water. OGTT = Oral Glucose Tolerance Test. QMR = Quantitative Magnetic Resonance.

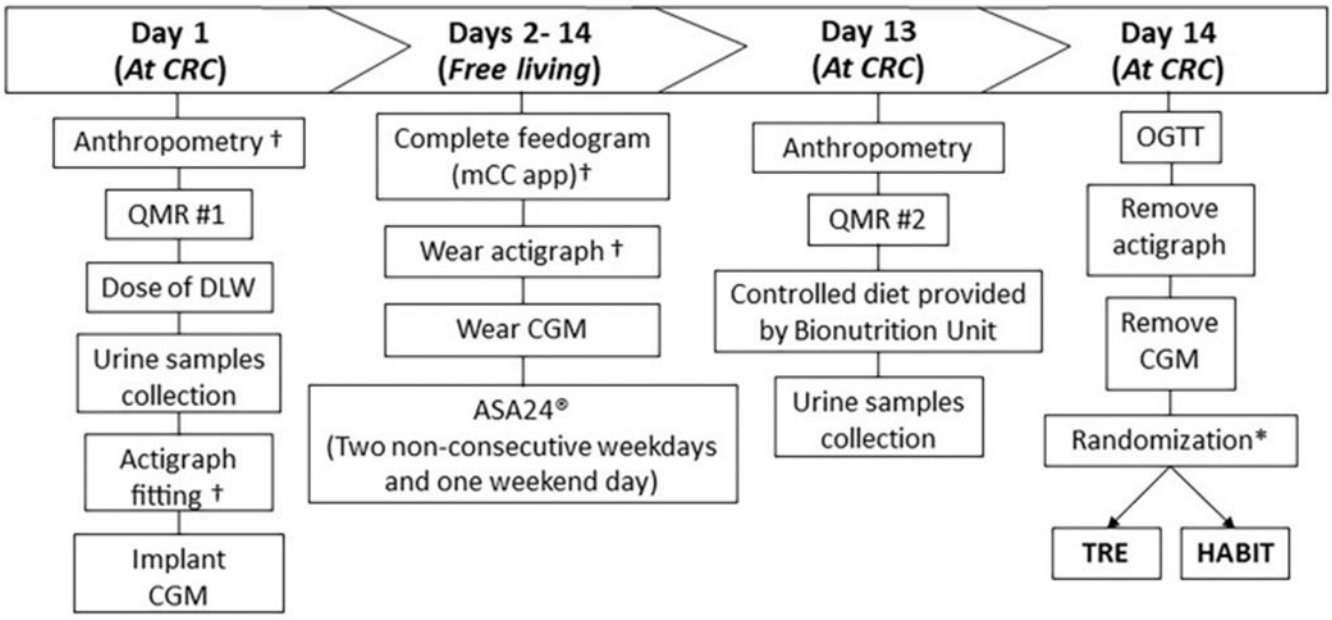

Fig. 3.

Timetable of study procedures during the 2-week baseline assessment.

* = All assessments are repeated during the last 2 weeks of 3 months, except randomization.

† = Assessments completed at 12 months. QMR = Quantitative Magnetic Resonance, DLW = Doubly Labelled Water, CGM = Continuous Glucose Monitoring, mCC = myCircadianClock, ASA24 = Automated Self-Administered 24-h, OGTT = Oral Glucose Tolerance Test, TRE = Time-Restricted Eating.

Table 1

Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
Age: 50–75 years old	Sleep disorder, e.g. known obstructive sleep apnea (OSA), severe OSA with apnea-hypopnea index >30 events/h, significant daytime symptoms of OSA, periodic limb movements of sleep, narcolepsy, severe insomnia (a score ≥ 15 on Insomnia Severity Index)
BMI ≥25 and ≤ 45 kg/m^2 with a diagnosis of prediabetes or T2D	Current shift work or recent shift work in the last 6 months
Fasting glucose ≥100 mg/dL, and/or HbA1c ≥5.7% and < 7.5%	Travel more than one time zone during the intervention
Treatment with metformin and/or diet-controlled if T2D	Significant organ system dysfunction/disease or evidence of active illness
Two or more of the following metabolic syndrome criteria: - Diagnosis of hypertension on stable medication regimen - Diagnosis of dyslipidemia on stable regimen - HDL cholesterol men <40 mg/dL and women <50 mg/dL - Waist circumference men: >102 cm (>40 40 in); women >88 cm (>35 in)	Use of dietary supplements and/or medications known to affect sleep, circadian rhythms, or metabolic Function
In possession of a smartphone	History of seizure disorder
Habitual prolonged eating window (≥14 h)	Habitual eating window <14 h
≥70% of days with logging adherence (2 or more log entries/day separated by at least 5 h), assessed during 2-week remote screening	Previous bariatric surgery or use of weight loss medication
Sleep duration ≥6 h, with habitual self-reported wake-up time > 5:00 am and < 11:00 am, and average self-reported bedtime before 2:00 am	History of or current significant food intake or psychiatric disorder (BDI score ≥ 29; BAI score ≥ 26)
Subject habitually eats breakfast	Excessive alcohol (women: >14 drinks/week; men: >21 drinks/week), smoking tobacco, or using illegal or recreational drugs
Weight stability within 5% for the 3 months preceding screening	Severe food allergies
Lives in the New York City metro area	Anemia (hemoglobin <10 g/dl and hematocrit <30%)
English fluency, since the smartphone application has not been translated	Unwilling/unable to provide informed Consent

BAI = Beck's Anxiety Inventory; BDI = Beck's Depression Inventory; BMI = Body Mass Index; HbA1c = glycated hemoglobin; HDL = High-Density Lipoprotein; OSA = Obstructive Sleep Apnea; T2D = Type 2 Diabetes.