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Time-restricted eating, caloric reduction, and unrestricted eating effects on weight and metabolism: a randomized trial

Niki Oldenburg[1] | Douglas G. Mashek[1] | Lisa Harnack[2] | Qi Wang[3] | Emily N. C. Manoogian[4] | Nicholas Evanoff[5] | Donald R. Dengel[5] | Abdisa Taddese[1] | Brad P. Yentzer[1] | Lesia Lysne[1] | Alison Wong[1] | Michelle Hanson[1] | Julie D. Anderson[1] | Alison Alvear[1] | Nicole LaPage[1] | Justin Ryder[6] | Krista Varady[7] | Zan Gao[8] | Suryeon Ryu[5] | Patrick J. Bolan[9] | Bryan Bergman[10] | Erika Helgeson[2] | Satchidananda Panda[4] | Lisa S. Chow[1]

[1]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA

[2]School of Public Health, University of Minnesota, Minneapolis, Minnesota, USA

[3]Clinical and Translational Science Institute, University of Minnesota, Minneapolis, Minnesota, USA

[4]Salk Institute for Biological Sciences, San Diego, California, USA

[5]College of Education and Human Development, University of Minnesota, Minneapolis, Minnesota, USA

[6]Department of Surgery, Northwestern University Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA

[7]College of Applied Health Sciences, University of Illinois, Chicago, Illinois, USA

[8]College of Education, Health, and Human Sciences, University of Tennessee, Knoxville, Tennessee, USA

[9]Department of Radiology, University of Minnesota, Minneapolis, Minnesota, USA

[10]School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Correspondence
Lisa S. Chow, Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, University of Minnesota, MMC 101, 420 Delaware St SE, Minneapolis, MN 55455, USA.
Email: chow0007@umn.edu

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Abstract

Objective: Metabolic improvements may precede weight loss. We compared the effects of self-selected 8-h time-restricted eating (TRE), 15% caloric restriction (CR), and unrestricted eating (UE) on weight, body composition, caloric intake, glycemic measures, and metabolic flexibility.

Methods: In this 12-week randomized-controlled trial, we measured weight (primary outcome), body composition (dual-energy x-ray absorptiometry/magnetic resonance imaging), caloric intake (24-h recall), metabolic flexibility (indirect calorimetry during hyperinsulinemic-euglycemic clamp), and glycemic measures (hemoglobin A1c, hyperinsulinemic-euglycemic clamp, continuous glucose monitoring).

Results: Of the 88 enrolled participants, 81 (92%) completed the trial (mean [SD], age, 43.2 [10.5] years, BMI, 36.2 [5.1] kg/m^2; 54.5% female, 84.1% White). Final

See Commentary, pg. 627.

eating windows were 9.8 h (95% CI: 9.0 to 10.6) for TRE, 12.9 h (95% CI: 11.9 to 13.9) for CR, and 11.8 h (95% CI: 11.0 to 12.7) for UE. Compared with UE ($n = 29$), weight changes were −1.4 kg (95% CI: −4.5 to 1.7; $p = 0.53$) with TRE ($n = 30$) and −2.5 kg (95% CI: −5.8 to 0.8; $p = 0.18$) with CR ($n = 29$). TRE showed lower metabolic flexibility than CR (−0.041 [95% CI: −0.080 to −0.002]). Weight, body composition, caloric intake, and glycemic measures were similar among groups. Eating window reduction correlated with decreased caloric intake and visceral fat.

Conclusions: In a 12-week intervention, TRE did not lead to significant improvements in weight, average body composition, or glycemic or metabolic measures compared with CR or UE.

INTRODUCTION

Nearly one-half of US adults have obesity [1]. Whereas caloric restriction (CR) remains the standard weight loss recommendation, counting calories presents time and numeracy challenges. Time-restricted eating (TRE) offers a simpler alternative, limiting eating to a 4- to 12-h daily window, typically 8 to 10 h, with ad libitum intake during that period [2].

Multiple studies [2–4], including our work [5], have demonstrated that TRE (∼8–10 h, ad libitum intake during window) up to 16 weeks reduces weight by ∼3% to 5%. Several randomized-controlled trials (RCT) have directly compared TRE with ad libitum intake relative to CR or unrestricted eating (UE) [6, 7]; these studies have reported similar weight reduction between TRE and CR (∼5% for TRE over 12 months in patients with obesity, ∼4% for TRE over 6 months in patients with type 2 diabetes [6, 7]). However, these TRE studies, which directly compare with CR and UE [6, 7], imposed a fixed eating window (i.e., 12–8 p.m.), which may be less accommodating than a self-selected eating window.

TRE has a daily, prolonged fasting window, whereas CR can be disassociated from prolonged fasting. Although preliminary evidence has indicated that TRE may reduce weight similarly compared with CR and significantly compared with UE [6, 7], weight loss may not necessarily parallel metabolic improvement [8], and, likewise, metabolic improvement may not necessarily parallel weight loss [4]. The impact of TRE-associated prolonged fasting on fat and glucose use, as assessed by indirect calorimetry or hyperinsulinemic-euglycemic clamps, in comparison with CR remains unknown. This is due to the lack of comprehensive metabolic studies that have compared TRE versus CR using these specific measurement tools. Therefore, we conducted an RCT comparing 12 weeks of TRE with CR and UE in patients with obesity and without diabetes. Owing to the prolonged fasting with TRE, we hypothesized that 12 weeks of TRE would present a viable alternative to CR with respect to reduction in weight, fat mass (FM), caloric intake, glycemic measures, and improvement of metabolic flexibility, i.e., the capacity to switch between glucose and fat oxidation.

Study Importance

What is already known?

- Time-restricted eating (TRE) represents an alternative to caloric restriction (CR) regarding weight loss.
- Weight loss may not necessarily parallel metabolic improvements, and metabolic improvements may not necessarily parallel weight loss.

What does this study add?

- In a 12-week TRE intervention, TRE shortened the eating window, with no significant improvements in weight, average body composition, glycemic measures, or metabolic flexibility compared with CR or unrestricted eating.
- Reduction of the eating window, whether by 1 h or 10%, was associated with reduction of caloric intake and visceral fat.

How might these results change the direction of research or the focus of clinical practice?

- Our study showed that 12 weeks of TRE (8 h self-selected) was insufficient to demonstrate clear metabolic improvements compared with CR; future TRE-based interventions should be longer than 12 weeks and could consider a shorter self-imposed eating window.
- Future diet-based interventions should explore individual response predictors, as well as personalization of interventions.

METHODS

Design overview

This 12-week RCT conducted at the University of Minnesota, Twin Cities (October 2020–2023) assigned participants 1:1:1 to

TRE (8-h self-selected eating window), CR (15% CR), or UE groups (control group, monitoring of usual food intake with no specific intervention). The study was approved by University of Minnesota's institutional review board (STUDY00008545), and the myCircadianClock (mCC) app was approved by the Salk institutional review board (15-0003). This study was registered at ClinicalTrials.gov (NCT04259632). All participants provided written informed consent prior to participation. Figure 1A outlines the study design.

Setting and participants

Participants between the ages of 18 and 65 years with a body mass index (BMI) of 30 to 55 kg/m^2 were recruited from the MHealth Fairview Health System in Minneapolis, Minnesota. Eligibility criteria required participants to self-report waking times between 5 and 9 a.m., sleep duration of 6 to 9 h, and stable weight ±5 lb for >3 months prior to enrollment. Participants also needed English proficiency and an mCC app compatible smartphone [3]. Additional inclusion criteria required at least 7 days of mCC app documentation: at least two daily eating events separated by ≥5 h, recorded >1 day/week, with a ≥12-h eating window (calculated from the eating window containing 95% of eating events).

Exclusion criteria (online Supporting Information, Protocol) were as follows: eating window <12 h; weight-affecting medications; shift work; major medical conditions; magnetic resonance imaging (MRI) contraindications; pregnancy/planned pregnancy; illiteracy; history of eating disorders; or screening-identified eating disorder [9].

Randomization and intervention

Computer-generated randomization in Research Electronic Data Capture (REDCap) used permutated blocks of three, stratified by sex and age (<45 vs. ≥45 years), to assign participants to the TRE, CR, or UE groups. The statistical team generated and stored the randomization sequence in REDCap prior to study initiation. Participants were unblinded, whereas outcome assessors remained blinded. Details are in online Supporting Information, Methods and Manual of Procedures.

TRE

TRE participants selected an 8-h daily eating window beginning the day after randomization. Those who found this challenging could initially use a 10-h window for 1 to 2 weeks before adopting the fixed 8-h window. The daily eating window timing could be adjusted with dietitian approval. Dietitians used behavioral therapy techniques, including motivational interviewing, goal setting, and mCC app-based self-monitoring, to promote adherence.

CR

The CR group aimed to reduce daily caloric intake by 15% below weight maintenance. This was chosen for several reasons. Studies have suggested that TRE with ad libitum intake reduces daily caloric intake by 270 to 300 kcal (5%–20%) [2, 10], which is comparable with our 15% CR target. We were also interested in a sustainable CR restriction program; in the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy-2 (CALERIE-2) study, a 2-year study of CR, the sustained CR decrease was 11.9% [11]. In order to calculate the targeted caloric goal, calorie requirements for weight maintenance were determined by calculating basal metabolic rate using the Mifflin-St Jeor equation [12], multiplying the basal metabolic rate value by an activity factor determined from baseline actigraphy, and then multiplying this calculated value by 0.85. Study dietitians created food-exchange plans using the "Choose Your Foods: Food Lists for Weight Management" [13] guide for calorie targets. Behavioral counseling included motivational interviewing, goal setting, and app-based tracking (mCC was preferred; MyFitnessPal was used as an alternative). CR participants were allowed to use either the mCC (preferred) or MyFitnessPal (alternative) app for food tracking during the CR intervention. However, all CR participants were asked to use the mCC app at end of intervention (Weeks 10–12) to ensure consistent measurement of eating occasions.

UE

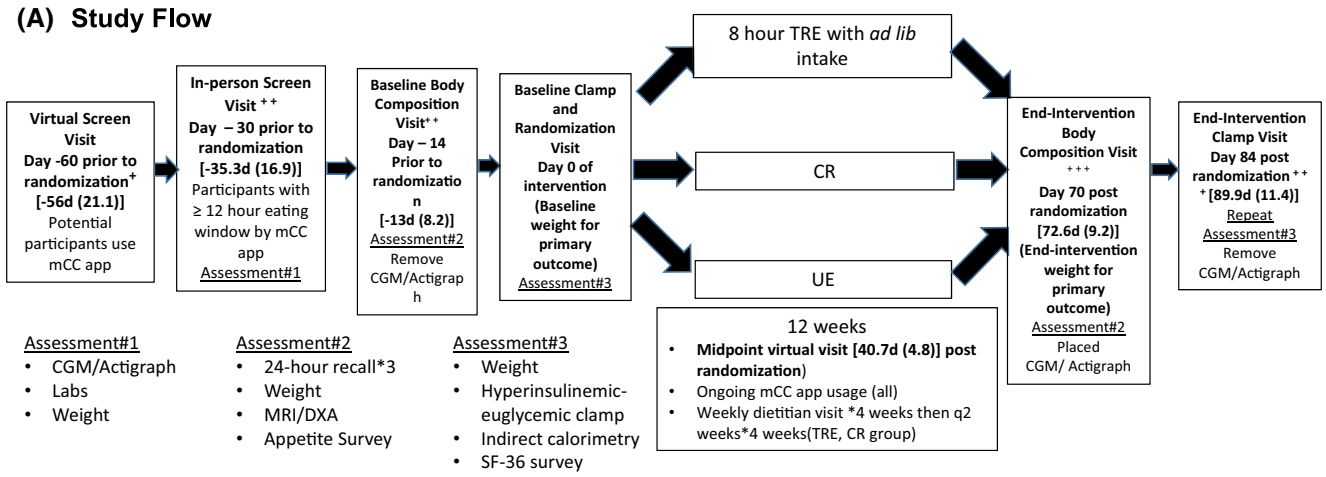
UE participants maintained their normal eating habits while tracking all dietary intake, excluding water and medications, using the mCC app. In order to enhance retention, they were offered dietary counseling after study completion.

Dietary intervention delivery

Study dietitians provided telephone-based counseling to participants. For the first 4 weeks, the TRE and CR groups had weekly sessions, followed by sessions every 2 weeks for the next 8 weeks. The TRE group was instructed to eat ad libitum during their self-selected 8-h daily window, whereas the CR group was guided to use a food-exchange system to decrease their daily calorie intake by 15%. The UE group had an initial session to reiterate mCC app use and emphasize the importance of tracking food intake.

Dietary intake monitoring

All participants, regardless of group, were instructed to record all of their oral intake, with the exception of water and medications, using the mCC app [3] during the entire study. An eating occasion was defined as any instance of oral intake of food or drink, including coffee, tea, diet drinks, and noncaloric beverages. In addition, an eating



+Virtual screening visit ~within 1 month from first in-person visit
++In-person preintervention evaluation ideally completed within 5 weeks prior to randomization
+++In-person post-intervention visits ideally completed within 3 weeks

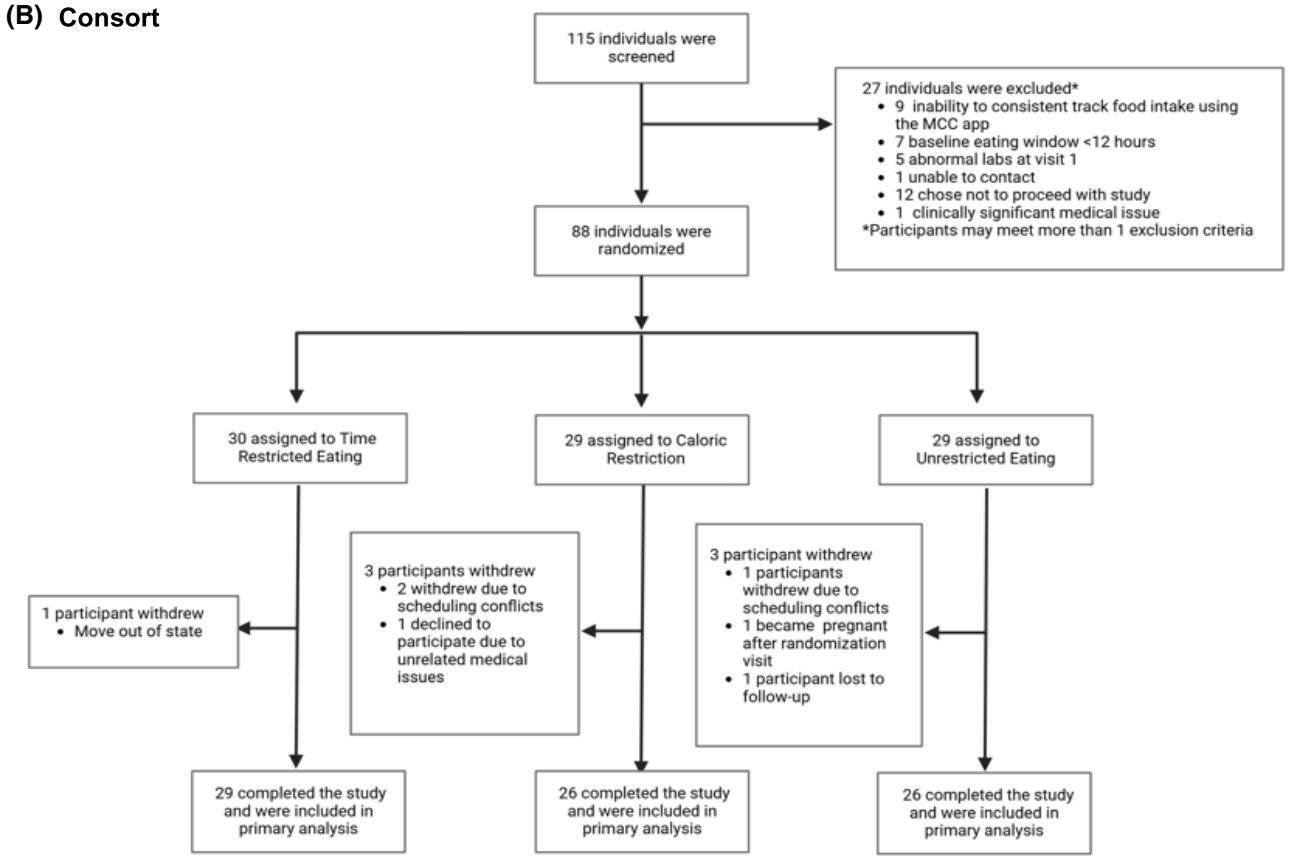


FIGURE 1 (A) Participant flow diagram and (B) CONSORT diagram. Means (SD) for days from randomization presented for all randomized individuals ($n = 88$). CGM, continuous glucose monitoring; CONSORT, Consolidated Standards of Reporting Trials; CR, caloric restriction; DXA, dual-energy x-ray absorptiometry; mCC, myCircadianClock; MRI, magnetic resonance imaging; TRE, time-restricted eating; UE, unrestricted eating. [Color figure can be viewed at wileyonlinelibrary.com]

occasion was defined as a distinct event when food or drink was documented ≥15 min separate from another eating occasion [14].

The study team evaluated the mCC data on a weekly basis and notified participants accordingly. The primary focus of this notification was to ensure adherence to mCC logging. For all groups, participants were deemed compliant with logging during follow-up if they logged at least two eating occasions, separated by 5 h, for a minimum of 4 days/week. For those in the TRE

group, the weekly notification also provided feedback on their adherence to the eating window.

The eating window was documented several ways. The first method defined the eating window as the time frame encompassing 95% of eating occasions. The second method determined the daily eating window by noting the time difference between the daily first and last meal recorded in the mCC app and then reporting the percentage of days with an eating window of 8 and 8.5 h. The third method evaluated the eating window independent of the mCC app. This was done by measuring the average daily eating period, using the 24-h dietary recalls, calculated as the time between the first and last reported eating events (collected at baseline [$n = 3$] and end of intervention [$n = 3$]; online Supporting Information, Manual of Procedures).

Outcomes and follow-up

The primary outcome was the absolute change in body weight between the randomization visit and the end-of-intervention body composition visit. Figure 1A shows timing of study measurements. Prespecified secondary outcomes included change in body composition (dual-energy x-ray absorptiometry [DXA]), caloric intake (24-h dietary recall), and metabolic flexibility (indirect calorimetry-based measurement of fat oxidation relative to glucose oxidation before the initiation of the clamp and just prior to the end of the low-dose and high-dose clamp) [15, 16].

Additional measures, as described in online Supporting Information Methods, include change in MRI-assessed body composition, resting energy expenditure by indirect calorimetry (measured in supine position: 30 min passive rest period, then 30 min assessment; TrueOne 2400 metabolic cart, ParvoMedics), insulin sensitivity (homeostatic model assessment of insulin resistance [HOMA-IR] and M-value by two-step hyperinsulinemic-euglycemic clamp, with first step low-dose insulin infusion at 10 mU/m^2/min for 2 h and second step high-dose insulin infusion at 40 mU/m^2/min for 2 h), continuous glucose monitoring (CGM) (blinded DexCom G6 Pro, DexCom, Inc.), actigraphy-based measures of physical activity and sleep (ActiGraph GT9X Link, ActiGraph LLC), and blood pressure. Study staff assessed appetite "in the moment" in fasted participants using a visual analogue scale [17] at the screening visit and at the end-of-intervention study visit. Study staff assessed quality of life using the 36-Item Short Form Health Survey (SF-36) survey, which reflects on health over the past year and specifically over the past 4 weeks [18, 19], at the randomization visit and at the end-of-intervention study visit. Study staff inquired about adverse events at each visit.

Statistical analysis

The study was powered to detect differences in weight loss for TRE and CR relative to UE while preserving type I error for pairwise comparisons across all three groups. Based on the preliminary data and the literature [5], we anticipated mean (standard deviation [SD]) weight loss of 3.6 (1.9) kg with TRE, 4 (2.5) kg with CR, and 1.5 (2.4) kg with UE. With $n = 24$ per group and $\alpha = 0.05/3$ to adjust for multiple comparisons, we estimated 80% power to detect the described difference in weight loss between TRE and UE and 85% power to detect the described difference in weight loss between CR and UE.

Data were analyzed by intention-to-treat. The primary efficacy analysis included all randomized individuals, with missing outcome measures imputed using multivariate imputation by chained equations. Change in outcomes was compared among the treatment arms using linear regression models, with pairwise comparisons conducted using Tukey method to account for multiple comparisons. As a sensitivity analysis, the primary outcome analysis was conducted using only individuals who had complete data for the outcome of interest (Table S1). An additional sensitivity analysis among study completers was conducted excluding one participant in the UE group who reported noncompliance and had extreme weight loss (i.e., 14.1 kg). For representing change in secondary measures with varying scales using forest plots, outcomes were transformed into z scores by subtracting the overall mean and dividing by the overall SD prior to fitting the linear regression model. The association between change in eating window and change in outcomes among study completers in the TRE and UE groups was assessed using linear regression models, and the CR arm was not included in these specific analyses because some participants preferred to document their eating occasions during the intervention using the MyFitnessPal app instead of the mCC app. The eating window was calculated using time frame encompassing 95% of eating occasions and change in eating window was calculated as difference in eating window from baseline (prior to randomization) and end of intervention (Weeks 10–12).

All analyses were carried out using R (version 4.3.1, R Foundation for Statistical Computing) or SAS (version 9.4, SAS Institute Inc.). Additional details are provided in Supporting Information Methods.

RESULTS

Trial participants

Of the 115 participants who consented, 100 (87%) were eligible to continue with the study, of whom 12 (10%) declined to continue. A total of 88 (88%) of the eligible participants were randomized, and 81 completed the primary outcome (Figure 1B). Withdrawal reasons included scheduling conflicts, unrelated medical issues and pregnancy, moving out of state, and nonresponse to contact by study staff. Participants were primarily female (54.5%) and White (87.5%), with a mean (SD) age of 43.2 (10.5) years and BMI of 36.2 (5.1) kg/m^2 (Table 1, Table S2). The mean (SD) baseline eating window was 14.4 (1.7) h (mCC app) and 12.5 (1.8) h (24-h dietary recall; Tables 1 and 2).

Intervention compliance

Table 2 documents the timing of the eating occasions reported by the mCC app during the intervention (Weeks 0–12) and at end of intervention (Weeks 10–12). This included the eating window, which covers 95% of eating events, the clock time when the eating window

TABLE 1 Baseline characteristics of randomized participants.

	TRE ($n = 30$)	CR ($n = 29$)	UE ($n = 29$)
Age, y	44.0 (11.5)	42.2 (9.6)	43.4 (10.7)
Gender			
Female	17 (56.7%)	15 (51.7%)	16 (55.2%)
Male	13 (43.3%)	14 (48.3%)	13 (44.8%)
Race			
American Indian/Alaska Native	0 (0%)	1 (3.4%)	0 (0%)
Asian	2 (6.7%)	2 (6.9%)	3 (10.3%)
Black or African American	2 (6.7%)	0 (0%)	1 (3.4%)
Mixed	2 (6.7%)	0 (0%)	0 (0%)
Native Hawaiian or other Pacific Islander	1 (3.3%)	0 (0%)	0 (0%)
White	23 (76.7%)	26 (89.7%)	25 (86.2%)
Weight, kg	107.2 (21.0)	109.9 (21.1)	109.0 (17.9)
BMI, kg/m^2	35.8 (5.7)	36.5 (5.5)	36.4 (4.1)
Baseline duration, d[a]	34.1 (14.5)	38.1 (22.9)	33.7 (11.4)
Eating window by mCC app, h/d	14.2 (1.0)	14.6 (2.4)	14.5 (1.3)
Systolic blood pressure, mm Hg	127.0 (12.5)	128.7 (12.7)	125.9 (15.3)
Diastolic blood pressure, mm Hg	79.6 (7.2)	80.8 (7.9)	80.8 (10.5)
Resting energy expenditure, kcal/d	1680.8 (233.8)	1835.3 (317.2)	1764.7 (306.2)
Diet components (24-h dietary recall)			
Eating window, h/d	12.5 (1.5)	12.3 (2.1)	12.8 (1.7)
Daily caloric intake, kcal/d	2184.7 (548.9)	2265.0 (719.9)	2389.6 (755.7)
Sugar-sweetened beverage intake, servings/d	0.4 (0.6)	0.3 (0.6)	1.1 (2.3)
HEI 2015 score[b]	53.0 (11.8)	52.0 (10.5)	53.7 (11.8)
Body composition by DXA			
Body fat, %	39.1 (7.5)	38.3 (8.6)	38.6 (6.5)
FFM, kg	64.8 (12.0)	67.6 (15.0)	67.0 (13.3)
FM, kg	42.3 (13.6)	42.3 (13.7)	42.0 (9.0)
VAT, kg	0.74 (0.24)	0.81 (0.21)	0.84 (0.33)
Body composition by DXA (female individuals: $n = 48$)	$n = 17$	$n = 15$	$n = 16$
Body fat, %	43.1 (5.8)	43.7 (6.8)	43.5 (2.7)
FFM, kg	56.6 (6.2)	56.5 (8.8)	57.5 (6.4)
FM, kg	44.2 (12.4)	46.7 (14.9)	44.6 (5.9)
VAT, kg	0.73 (0.24)	0.77 (0.17)	0.86 (0.31)
Body composition by DXA (male individuals: $n = 40$)	$n = 13$	$n = 14$	$n = 13$
Body fat, %	33.8 (6.2)	31.7 (5.2)	32.5 (4.5)
FFM, kg	75.1 (9.2)	79.4 (10.6)	78.4 (10.2)
FM, kg	39.9 (15.3)	37.6 (10.9)	38.8 (11.2)
VAT, kg	0.75 (0.25)	0.85 (0.24)	0.77 (0.42)
Body composition by MRI[c]			
Hepatic fat, %	6.5 (6.8)	11.3 (9.3)	12.0 (9.6)
SAT, cm^2	405.4 (163.3)	417.0 (156.8)	394.7 (122.9)
VAT, cm^2	152.8 (83.6)	181.1 (70.5)	215.0 (94.1)
SAT/VAT ratio	3.87 (3.45)	2.84 (2.28)	2.31 (1.60)
Body composition by MRI[c] (female individuals: $n = 48$)	$n = 17$	$n = 15$	$n = 16$
Hepatic fat, %	5.9 (4.5)	9.2 (9.3)	9.9 (8.8)
SAT, cm^2	437.3 (145.8)	485.7 (142.5)	432.6 (126.6)

TABLE 1 (Continued)

	TRE ($n = 30$)	CR ($n = 29$)	UE ($n = 29$)
VAT, cm^2	132.2 (78.8)	152.4 (44.8)	179.2 (68.8)
SAT/VAT ratio	4.91 (4.02)	3.72 (2.58)	2.92 (1.85)
Body composition by MRI[c] (male individuals: $n = 40$)	$n = 13$	$n = 14$	$n = 13$
Hepatic fat, %	7.3 (9.2)	14.0 (9.0)	14.6 (10.3)
SAT, cm^2	362.9 (181.8)	323.2 (127.7)	346.4 (104.2)
VAT, cm^2	180.3 (85.0)	220.2 (81.9)	260.4 (105.0)
SAT/VAT ratio	2.49 (1.88)	1.63 (0.98)	1.53 (0.72)
Glycemic measures	$n = 30$	$n = 29$	$n = 29$
HbA1c, %	5.5 (0.4)	5.4 (0.3)	5.6 (0.4)
HOMA-IR	3.7 (2.2)	4.0 (2.3)	5.6 (5.8)
Fasting glucose, mg/dL	95.5 (7.6)	91.4 (8.0)	99.2 (12.6)
Fasting insulin, mU/L	15.7 (9.4)	17.9 (9.1)	22.2 (19.6)
M-value from clamp low-dose infusion, mg glucose/kg FFM/min	2.4 (1.4)	2.4 (1.8)	2.2 (2.0)
M-value from clamp high-dose infusion, mg glucose/kg FFM/min	10.5 (5.0)	7.5 (4.2)	7.7 (5.0)
Metabolic flexibility at end of low-dose clamp	0.04 (0.05)	0.03 (0.05)	0.02 (0.03)
Metabolic flexibility at end of high-dose clamp	0.12 (0.07)	0.08 (0.05)	0.08 (0.04)
Lipid profile			
Fasting HDL, mg/dL	52.2 (13.5)	49.0 (15.6)	48.9 (11.6)
Fasting triglycerides, mg/dL	115.2 (58.9)	166.6 (84.0)	134.4 (52.0)
Fasting LDL, mg/dL	111.3 (31.9)	119.3 (35.3)	116.2 (38.5)

Note: Data are presented as *n* (%) or means (SD).
Abbreviations: CR, caloric restriction; DXA, dual-energy x-ray absorptiometry; FM, fat mass; FFM, fat-free mass; HEI, Healthy Eating Index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein, mCC, myCircadianClock; MRI, magnetic resonance imaging; SAT, subcutaneous adipose tissue; TRE, time-restricted eating; UE, unrestricted eating; VAT, visceral adipose tissue.
[a]The baseline duration refers to the duration of time between the first in-person visit and the randomization visit.
[b]An ideal overall HEI score of 100 reflects the set of foods aligning with key dietary recommendations and dietary patterns published in the *Dietary Guidelines for Americans* [21].
[c]A single slice at L3 served as the representative slice for MRI-based measures.

started and ended, and the percentage of days during which participants ate within an 8.5-h window, a more realistic window given variability in eating timing, as well as within an 8-h window.

Eating window

According to the 24-h dietary recall, the mean eating window at end of intervention was 9.8 h (95% CI: 9.0–10.6) with TRE; this was significantly lower than CR (12.9 h [95% CI: 11.9–13.9]) or UE (11.8 h [95% CI: 11.0–12.7]). The eating windows between the CR and UE groups were not significantly different.

According to the mCC app (Table 2), the TRE group's eating window during the intervention (12 weeks) was 10.0 h (95% CI: 9.2–10.9). In the final 2 weeks of the intervention, the TRE group's eating window was 9.1 h (95% CI: 8.4–9.7), an average reduction of 5.1 h (95% CI: 4.5–5.7) relative to baseline. Adherence to the daily 8-h eating window averaged 63.8% (95% CI: 50.1%–77.6%) of days during the intervention and 73.4% (95% CI: 60.7%–86.1%) of days at end of intervention. When considering a daily 8.5-h eating window, which presents a more realistic window to accommodate for fluctuation in daily eating times, adherence in the TRE group averaged 67.9% (95% CI: 54.8%–81.0%) of days during the intervention and 77.7% (95% CI: 66.3%–89.1%) of days at end of intervention.

Reduction in caloric intake

The 24-h dietary recall was used to assess reduction in caloric intake. The average percentage change in caloric intake among study completers was −16.5% of kilocalories (95% CI: −24.8% to −8.2%) for TRE ($n = 28$), −8.7% of kilocalories (95% CI: −21.8% to 4.5%) for CR ($n = 19$), and −1.2% of kilocalories (95% CI: −12.7% to 10.2%) for UE ($n = 26$). The absolute reduction in caloric intake was not significantly different among groups (Table 3).

Dietitian visit attendance

Participants in the TRE and CR groups completed a similar number of counseling sessions with study dietitians. Owing to the simplicity

TABLE 2 Eating timing as documented by the mCC app.

	TRE	CR	UE
Baseline			
n	30	29	29
Duration in days	56.9 (48.9–64.8)	59.8 (49.8–69.8)	54.3 (48.8–59.9)
Beginning of the eating interval	7:26 (6:46–8:05)	7:33 (6:10–7:49)	7:19 (6:32–8:05)
End of the eating interval	21:28 (20:50–22:26)	21:19 (20:49–22:12)	21:32 (21:01–22:28)
95% eating interval	14.2 (13.8–14.6)	14.6 (13.7–15.5)	14.5 (14.0–15.0)
% days within 8.5 h	15.1 (10.9–19.4)	20.8 (16.2–25.4)	16.3 (10.5–22.0)
% days within 8 h	11.1 (7.8–14.4)	15.2 (11.8–18.7)	12.7 (8.0–17.4)
Intervention			
n	30	22[a]	28
Duration in days	87.9 (82.7–93.1)	91.0 (84.7–97.4)	86.3 (78.8–93.8)
Beginning of the eating interval	9:08 (7:55–11:01)	6:37 (6:10–7:41)	7:28 (6:36–7:55)
End of the eating interval	19:19 (18:50–20:11)	20:38 (20:02–21:38)	21:18 (20:24–22:18)
95% eating interval	10.0 (9.2–10.9)	14.6 (13.3–16.0)	14.0 (13.5–14.6)
% days within 8.5 h	67.9 (54.8–81.0)	29.6 (21.8–37.4)	21.7 (14.8–28.5)
% days within 8 h	63.8 (50.1–77.6)	25.4 (17.8–33.0)	17.6 (11.6–23.7)
End of intervention (last 2 wk of the intervention)			
n	27	10[b]	23
Duration in days	15.0 (15.0–15.0)	15.0 (15.0–15.0)	15.0 (15.0–15.0)
Beginning of the eating interval	10:30 (8:11–11:02)	7:35 (6:35–7:59)	7:27 (6:33–8:17)
End of the eating interval	19:00 (18:23–19:49)	20:18 (19:58–21:02)	21:04 (19:55–22:01)
95% eating interval	9.1 (8.4–9.7)	13.2 (12.3–14.1)	13.6 (12.9–14.3)
% days within 8.5 h	77.7 (66.3–89.1)	28.2 (13.7–42.8)	19.5 (12.6–26.4)
% days within 8 h	73.4 (60.7–86.1)	19.9 (5.2–34.6)	15.9 (9.3–22.4)
Change in eating window relative to baseline in hours[c]	−5.1 (−5.7 to −4.5)	−0.8 (−1.8 to 0.2)	−0.7 (−1.4 to −0.1)

Note: For each time period, participants with 4 or more good logging days are included. Data presented are medians (IQR) for time and means (95% CI) for all other measures. Means were estimated among study completers using linear regression models.

Abbreviations: CR, caloric restriction; mCC, myCircadianClock; TRE, time-restricted eating; UE, unrestricted eating.

[a]Participants in the CR group were allowed to use MyFitnessPal to monitor their CR during the intervention if they declined using the mCC app.

[b]Participants in the CR group were specifically instructed by study staff to use the mCC app (regardless of MyFitnessPal usage) to document eating occasions during the end-of-intervention period.

[c]Change in eating window is comparing the 95% eating window at end of intervention relative to baseline.

of the intervention, the TRE group was permitted to have less allocated dietitian time as noted in the protocol. Compared with the CR group (36.2 min [95% CI: 33.1–39.3]), the TRE group spent less time (20.9 min [95% CI: 17.8–23.9]) per dietitian visit and less overall dietitian time (42% less) during the intervention (Table S3).

Weight loss and body composition

Among all randomized participants, the mean weight loss was −1.4 kg (95% CI: −4.5 to 1.7; $p = 0.53$) with TRE ($n = 29$) and −2.5 kg (95% CI: −5.8 to −0.8; $p = 0.18$) with CR ($n = 29$) compared with UE ($n = 29$). The mean difference between TRE and CR was 1.1 kg (95% CI: −2.0 to 4.2; $p = 0.69$; Figure 2, Table 3, Figure S1). There was no difference in body composition measures among the groups as measured by DXA or MRI.

In a sensitivity analysis among study completers, CR participants had greater total FM loss as measured by DXA and percentage hepatic fat and subcutaneous adipose tissue as measured by MRI compared with UE (Tables S1, S3–S5). In a sensitivity analysis among study completers with removal of one participant from the UE group with extreme weight loss (i.e., 14.1 kg and reported noncompliance), the weight loss for TRE ($n = 29$) and CR ($n = 26$) compared with UE ($n = 25$) was more pronounced at −2.2 kg (95% CI: −3.9 to −0.5) and −2.7 kg (95% CI: −4.5 to −0.9), respectively (Table S4).

Metabolic measures

TRE resulted in lower metabolic flexibility (−0.041 [95% CI: −0.08 to −0.002]) than CR (Table 3). Neither TRE nor CR had any differences

TABLE 3 Change in weight, caloric intake, body composition, and metabolic flexibility from baseline and among intervention groups.

	Change from baseline (95% CI)			Difference among groups (95% CI)		
	TRE ($n = 30$)	CR ($n = 29$)	UE ($n = 29$)	TRE vs. CR	TRE vs. UE	CR vs. UE
Primary outcome						
Weight, kg	−3.0 (−4.8 to −1.3)	−4.1 (−6.0 to −2.2)	−1.6 (−3.6 to 0.3)	1.1 (−2.0 to 4.2) $p = 0.69$	−1.4 (−4.5 to 1.7) $p = 0.53$	−2.5 (−5.8 to 0.8) $p = 0.18$
Secondary outcomes						
Caloric intake, kcal/d	−425.1 (−692.0 to −158.3)	−217.1 (−559.1 to 124.9)	−87.6 (−368.0 to 192.9)	−208.0 (−729.1 to 313.0)	−337.6 (−802.8 to 127.6)	−129.5 (−650.4 to 391.3)
Body composition by DXA						
Body fat, %	−0.6 (−1.7 to 0.5)	−1.0 (−2.1 to 0.2)	−0.3 (−1.4 to 0.9)	0.4 (−1.5 to 2.2)	−0.3 (−2.2 to 1.5)	−0.7 (−2.6 to 1.2)
FFM, kg	−0.6 (−1.7 to 0.5)	−1.0 (−2.1 to 0.1)	−0.6 (−1.7 to 0.5)	0.4 (−1.4 to 2.3)	−0.0 (−1.8 to 1.8)	−0.4 (−2.3 to 1.5)
FM, kg	−2.0 (−3.4 to −0.6)	−2.9 (−4.4 to −1.3)	−0.8 (−2.4 to 0.7)	0.9 (−1.6 to 3.4)	−1.2 (−3.6 to 1.3)	−2.1 (−4.7 to 0.5)
VAT, kg	−0.040 (−0.099 to 0.019)	−0.033 (−0.094 to 0.028)	0.030 (−0.034 to 0.094)	−0.007 (−0.109 to 0.095)	−0.070 (−0.172 to 0.032)	−0.063 (−0.168 to 0.043)
Metabolic flexibility						
M-value from clamp low-dose infusion, mg glucose/kg FFM/min	0.2 (−0.6 to 0.9)	0.1 (−0.8 to 1.0)	−0.3 (−1.1 to 0.5)	0.1 (−1.3 to 1.5)	0.4 (−0.9 to 1.7)	0.3 (−1.2 to 1.8)
M-value from clamp high-dose infusion, mg glucose/kg FFM/min	−0.8 (−2.7 to 1.1)	0.8 (−1.4 to 3.0)	−0.6 (−2.6 to 1.5)	−1.6 (−5.0 to 1.8)	−0.2 (−3.5 to 3.0)	1.4 (−2.3 to 5.1)
Metabolic flexibility at end of low-dose clamp	−0.004 (−0.030 to 0.023)	0.009 (−0.022 to 0.039)	0.007 (−0.021 to 0.036)	−0.013 (−0.061 to 0.036)	−0.011 (−0.058 to 0.036)	0.001 (−0.050 to 0.053)
Metabolic flexibility at end of high-dose clamp	−0.017 (−0.039 to 0.005)	0.024 (0.000 to 0.047)	−0.005 (−0.029 to 0.019)	−0.041 (−0.080 to −0.002)	−0.012 (−0.050 to 0.026)	0.029 (−0.013 to 0.071)

Note: Means were estimated using linear regression model. Pooled results across 50 imputations are presented. 95% CI for pairwise comparisons were adjusted using Tukey method.
Abbreviations: CR, caloric restriction; DXA, dual-energy x-ray absorptiometry; FM, fat mass; FFM, fat-free mass; TRE, time-restricted eating; UE, unrestricted eating; VAT, visceral adipose tissue.

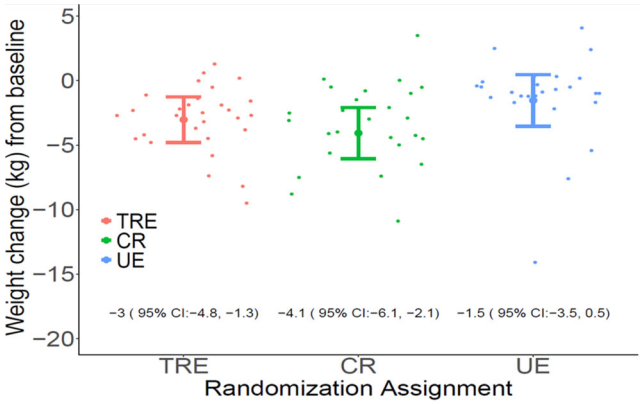


FIGURE 2 Body weight change from baseline by treatment group. Means and 95% CI were estimated using linear regression model. Pooled results across 50 imputations are presented. Individual data points from study completers are presented. CR, caloric restriction; TRE, time-restricted eating; UE, unrestricted eating.

in resting energy expenditure, lipid profile, or glycemic measures, as assessed by hemoglobin A1c [HbA1c], hyperinsulinemic-euglycemic clamp, HOMA-IR [20], or CGM measures of time-in-range (Table 3, Figure 3), compared with UE. Among study completers, the CGM-measured percentage time ≥180 mg/dL decreased and the percentage time between 70 and 180 mg/dL increased with CR compared with UE (Tables S3 and S5).

Dietary measures

Neither CR nor TRE altered caloric intake relative to UE (Table 3, Tables S1 and S4). Changes in dietary quality, as measured by the Healthy Eating Index [21], or sugar-sweetened beverage intake (servings per day) did not differ among interventions (Figure 4, Tables S3 and S5).

Lifestyle measures

Changes in actigraphy-measured physical activity distribution, sleep duration, and sleep quality did not differ among interventions (Figure 4, Tables S3 and S5). Changes in survey-assessed appetite and quality of life among study completers were not different among interventions (Figure S2, Table S3).

Sensitivity analysis with removal of one participant from the UE group with extreme weight loss (i.e., 14.1 kg and reported noncompliance) provided an additional finding that TRE reduced hunger relative to CR (Table S5); other findings remained unchanged.

Effect of eating window duration on outcomes

Table 4 reports the relationships of changes in the mCC-measured eating window with outcomes. We compared the TRE versus UE groups for a more direct evaluation of the eating window effects on outcomes. There was no effect of decreasing the eating window on weight. A decrease in the eating window, as measured by either absolute (1 h) change or relative (10%) change from the mCC app, was associated with a decrease in caloric intake and visceral adipose tissue accumulation.

Adverse events

Adverse events did not differ among groups (one per group, three events total). No serious adverse events were reported (Table S6).

DISCUSSION

Prior research has reported that TRE produces comparable results with CR regarding weight loss, HbA1c levels, and CGM outcomes, although the effects of TRE on more sophisticated metabolic measures such as energy expenditure, metabolic flexibility, and insulin sensitivity have not yet been studied, to our knowledge. Using an intention-to-treat approach with imputed outcomes for missing measures, we found that a 12-week TRE intervention (8 h, self-selected eating window) in patients with obesity shortened the eating window and reduced weight relative to baseline but did not improve weight, caloric intake, body composition, resting energy expenditure, metabolic flexibility, or glycemic measures compared with CR or UE. In a sensitivity analysis using the results from study completers, we found that CR significantly reduced weight relative to UE, and both TRE and CR reduced weight after excluding a participant from the UE group with extreme weight loss. Additional analysis found that reducing the eating window by either 1 h or 10% correlated with decreased caloric intake and visceral fat. No serious adverse events occurred in any group.

Among all randomized participants, including early study dropouts, we found no significant differences in most of our metabolic outcomes among the TRE, CR, and UE groups. Our observed TRE-associated weight loss is similar to that of published literature [2, 4, 5, 7, 10]. Our study uniquely uses comprehensive metabolic assessments, i.e., indirect calorimetry, hyperinsulinemic-euglycemic clamp, and MRI-based fat measures, to compare the fasting effects of TRE with CR and to identify any early metabolic changes across the TRE, CR, and UE groups. We evaluated self-selected TRE versus CR and UE, as this approach better represents real-world TRE implementation than fixed TRE intervals, as previously published [6, 7]. Although our findings do not support the idea that 12 weeks of self-selected TRE is sufficient to enhance metabolic flexibility, preferentially reduce FM, or improve glycemic measures relative to CR or UE, the study period (12 weeks) and studied population (with obesity and without diabetes) may not be sufficient to capture these effects. Our novel observation that reducing the eating window

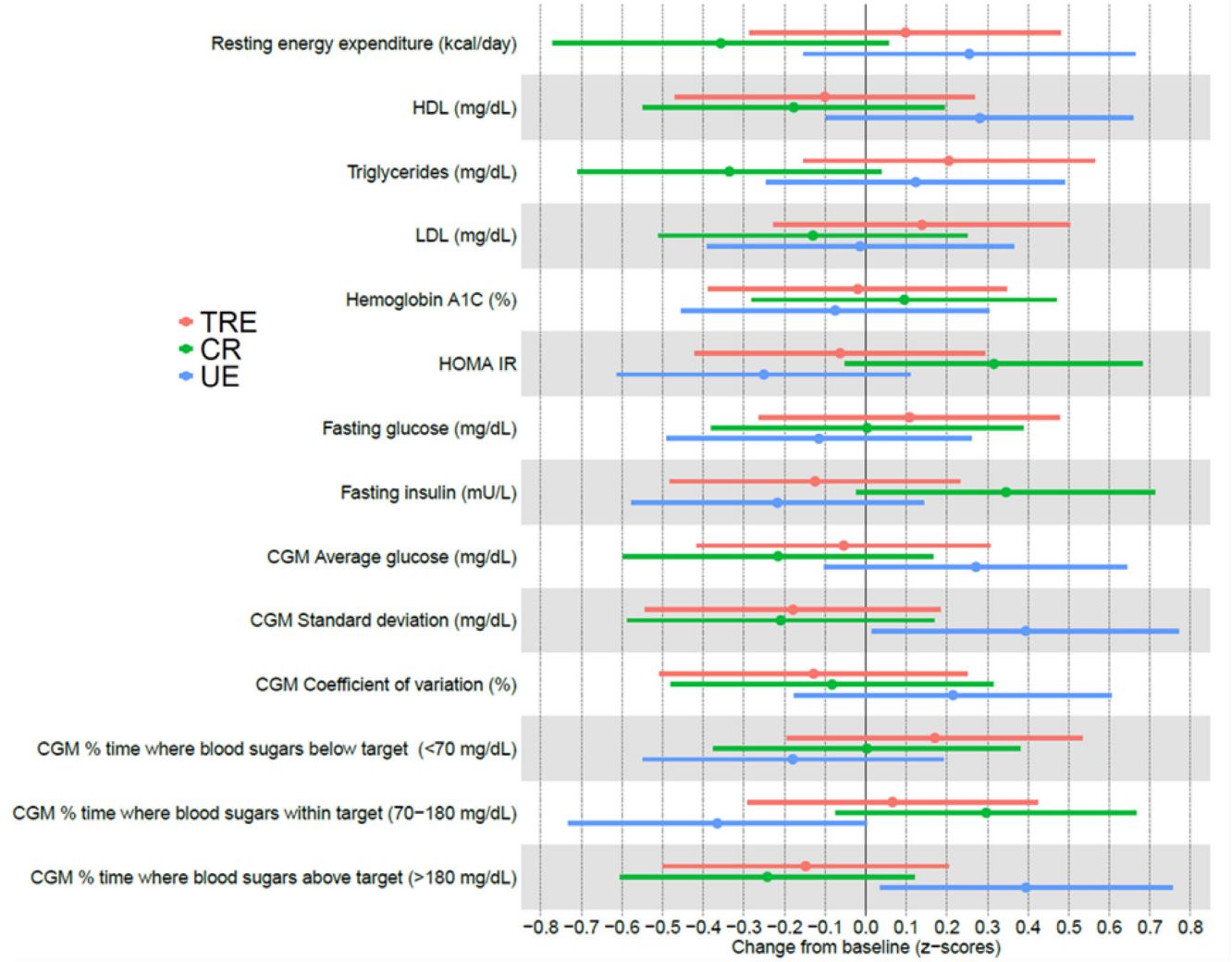


FIGURE 3 Forest plot of change in cardiometabolic measures (standardized to *z* scores) from baseline. Means and 95% CI were estimated using linear regression models. Pooled results across 50 imputations are presented. Error bars represent 95% CI. Measures were transformed into *z* scores by subtracting the overall mean and dividing by the overall SD prior to model fitting. CGM, continuous glucose monitoring; CR, caloric restriction; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; TRE, time-restricted eating; UE, unrestricted eating.

correlated with decreased caloric intake and visceral fat suggests that a shorter eating window and longer interventions may yield stronger results. A 12-month study comparing TRE, CR (25% reduction), and UE in participants without diabetes showed similar loss of FM and visceral fat between TRE and CR, although only the TRE group significantly lost FM relative to the UE group at 6 and 12 months [6]. A 6-month study comparing TRE with CR (25% reduction) versus UE in patients with type 2 diabetes mellitus showed similar improvements in HbA1c between TRE and CR, with TRE producing greater weight loss than CR or UE [7].

Our study strengthens and extends prior research comparing TRE with CR. We designed the interventions with sustainable intentions by allowing participants to self-select their eating window, unlike the fixed window in other studies [6, 7], to facilitate compliance (i.e., TRE) and a 15% reduction in caloric intake, which has been shown to be sustainable over 2 years [11]. Instead of recording food intake using repeated 7-day food records [6, 7], our participants used the mCC app to prospectively document eating occasions during the entire study, with independent confirmation via 24-h dietary recalls at baseline and at end of intervention. Moving beyond weight and body composition (i.e., DXA, MRI), we assessed metabolic flexibility and insulin sensitivity by the hyperinsulinemic-euglycemic clamp, neither of which has yet been reported in an RCT comparing TRE with CR, to our knowledge. Finally, we objectively measured physical activity using actigraphy and resting energy expenditure using indirect calorimetry and noted no difference in physical activity or resting energy expenditure among groups.

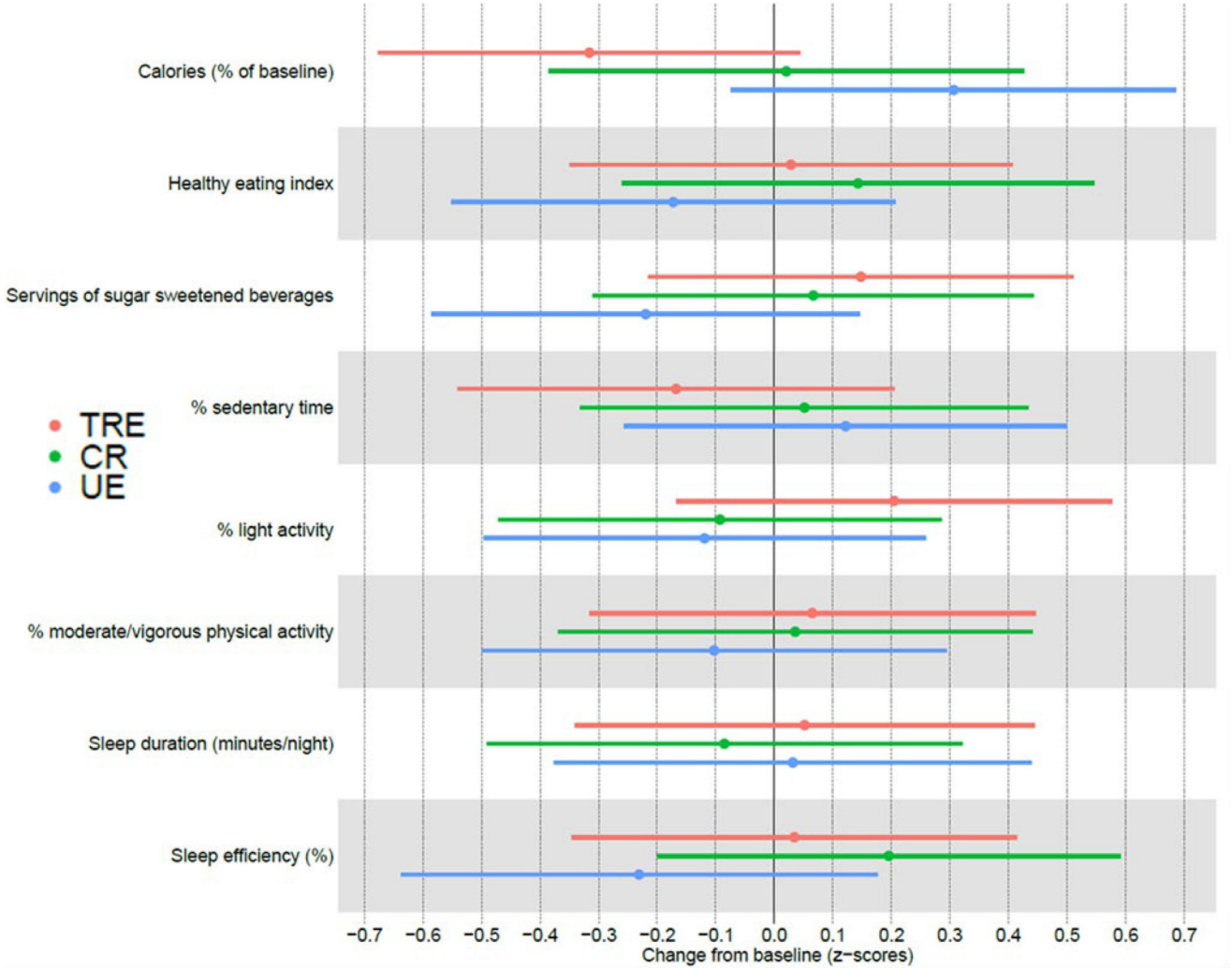


FIGURE 4 Forest plot of change in dietary and lifestyle measures (standardized to *z* scores) from baseline. Means and 95% CI were estimated using linear regression models. Pooled results across 50 imputations are presented. Error bars represent 95% CI. Measures were transformed into *z* scores by subtracting the overall mean and dividing by the overall SD prior to model fitting. CR, caloric restriction; TRE, time-restricted eating; UE, unrestricted eating.

We acknowledge several limitations. We required consistent use of the mCC app before randomization. This may introduce bias by selecting participants with high logging adherence and mobile technology skills, potentially limiting generalizability. We applied the TRE and CR interventions in the free-living setting, with intervention adherence potentially tempering the study results. Although the TRE group was asked to maintain an 8-h eating window, the achieved window was ∼9 to 10 h, which is similar to that of published studies [4, 5]. There was a discrepancy between the reduction in eating window (∼2–3 h relative to CR and UE) as measured by the 24-h dietary recall versus the mCC app (∼4 h relative to CR and UE), which is likely due to measurement differences, as the 24-h dietary recall captured 3 days of self-reported meal timing at baseline and at end of intervention, whereas the mCC app defined the eating windows containing 95% of eating events at baseline and at end of intervention; our observed changes in eating window duration and weight loss still align with those of previous TRE studies [2, 4, 5, 7, 10]. We selected a 15% caloric reduction for the CR group based on evidence of long-term sustainability. However, the achieved caloric reduction was ∼9%, which may have contributed to the null findings among the CR, TRE, and UE groups. Our measures of metabolic flexibility and resting energy expenditure were acquired under standardized, controlled conditions; this may not represent the effects of TRE or CR on these measures in the free-living environment. Finally, the 12-week study duration limits insights into long-term metabolic adaptations, particularly as extended duration of the TRE intervention (≥6 months) reduces weight and fat relative to UE [6, 7].

TABLE 4 Relationships of changes in eating window as documented by the mCC app with changes in weight, caloric intake, body composition, and metabolic measures for study completers in the TRE and UE arms[a].

	1-h decrease in eating window[b]	10% decrease in eating window[b]
Primary outcome		
Weight, kg[c]	−0.21 (−0.54 to 0.12)	−0.33 (−0.82 to 0.17)
Secondary outcomes		
Caloric intake, kcal/d[d]	−106.91 (−167.23 to −46.6)	−168.38 (−257.87 to −78.89)
Body composition by DXA[e]		
Body fat, %	0.05 (−0.18 to 0.28)	0.09 (−0.25 to 0.44)
FFM, kg	−0.09 (−0.31 to 0.12)	−0.18 (−0.51 to 0.14)
FM, kg	−0.01 (−0.35 to 0.34)	−0.02 (−0.54 to 0.5)
VAT, kg	−0.015 (−0.031 to 0)	−0.025 (−0.047 to −0.002)
Metabolic measures		
M-value from clamp low-dose infusion, mg glucose/kg FFM/min[f]	0.08 (−0.13 to 0.29)	0.11 (−0.22 to 0.43)
M-value from clamp high-dose infusion, mg glucose/kg FFM/min[f]	0.11 (−0.46 to 0.69)	0.17 (−0.7 to 1.05)
Metabolic flexibility at end of low-dose clamp[g]	−0.001 (−0.006 to 0.004)	−0.001 (−0.009 to 0.007)
Metabolic flexibility at end of high-dose clamp[g]	0.002 (−0.003 to 0.007)	0.003 (−0.004 to 0.011)

Abbreviations: DXA, dual-energy x-ray absorptiometry; FM, fat mass; FFM, fat-free mass; mCC, myCircadianClock; TRE, time-restricted eating; UE, unrestricted eating; VAT, visceral adipose tissue.

[a]Only the TRE and UE arms were included because these arms were instructed to document all eating occasions for the duration of the study using the mCC app.

[b]Eating window calculated using 95% method (see online Supporting Information Methods). Change in eating window calculated as difference in eating window from baseline (prior to randomization) and at end of intervention (Weeks 10–12). Only participants with 4 or more good logging days at baseline and at end of intervention are included.

[c]$n = 27$ for TRE and $n = 20$ for UE.

[d]$n = 25$ for TRE and $n = 19$ for UE.

[e]$n = 27$ for TRE and $n = 20$ for UE.

[f]$n = 22$ for TRE and $n = 17$ for UE.

[g]$n = 22$ for TRE and $n = 16$ for UE.

CONCLUSION

Compared with CR, TRE results in daily prolonged fasting. Although the hypothesized metabolic benefits associated with 12 weeks of TRE beyond weight loss were not observed, shortening the eating window reduced caloric intake and visceral fat. This suggests that extending TRE beyond 12 weeks may yield benefits, which is consistent with previous research [6, 7]. Key questions remain regarding optimal eating window duration and whether individual responses to dietary interventions, including changes in weight, body composition, metabolism, and glycemic measures, can be predicted and personalized for specific outcomes. The deep phenotyping and extensive characterization of the participants in this study set the foundation for these future analyses.O

AUTHOR CONTRIBUTIONS

Niki Oldenburg, Douglas G. Mashek, and Lisa S. Chow designed research; Niki Oldenberg, Lisa Harnack, Nicholas Evanoff, Donald R. Dengel, Abdisa Taddese, Brad P. Yentzer, Lesia Lysne, Alison Wong, Alison Alvear, Nicole LaPage, Suryeon Ryu, and Patrick J. Bolan conducted research; Niki Oldenberg, Douglas G. Mashek, Lisa Harnack, Qi Wang, Emily M. C. Manoogian, Zan Gao, Suryeon Ryu, Patrick J. Bolan, and Erika Helgeson analyzed the data; Niki Oldenberg, Douglas G. Mashek, and Lisa S. Chow wrote the paper; Niki Oldenberg, Douglas G. Mashek, Lisa Harnack, Qi Wang, Emily M. C. Manoogian, Nicholas Evanoff, Donald R. Dengel, Abdisa Taddese, Brad P. Yentzer, Lesia Lysne, Alison Wong, Alison Alvear, Nicole LaPage, Justin Ryder, Kristina Varady, Zan Gao, Suryeon Ryu, Patrick J. Bolan, Bryan Bergman, Erika Helgeson, Satchidananda Panda, Lisa S. Chow, Michelle Hanson, and Julie D. Anderson edited the paper and provided intellectual input; Lisa S. Chow has primary responsibility for final content; and all authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Satchidananda Panda has authored a book "The Circadian Code" for which he receives author royalty and specifically recommends time-restricted eating. The other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT04259632.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Nicholas Evanoff https://orcid.org/0000-0001-5616-5857
Krista Varady https://orcid.org/0000-0002-9279-9934
Lisa S. Chow https://orcid.org/0000-0002-6210-2307

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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