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Time-Restricted Eating in Adults with Metabolic Syndrome: A Randomized Control Trial (The TIMET Study)

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Abstract

Background.

Time-restricted eating (TRE), limiting daily dietary intake to a consistent 8–10 hours without mandating calorie reduction, may provide cardiometabolic benefits.

Objective.

To determine the effects of TRE as a lifestyle intervention combined with current standard-of-care treatments on cardiometabolic health in adults with metabolic syndrome.

Design.

Randomized control trial. [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04057339): [NCT04057339](https://clinicaltrials.gov/ct2/show/study/NCT04057339).

Setting.

Clinical research institute.

Participants.

Adults with metabolic syndrome including elevated fasting glucose or HbA1c (pharmacotherapy allowed).

Interventions.

Participants were randomized to standard-of-care nutritional counseling alone (SOC) or combined with a personalized 8–10 h TRE intervention (≥ 4 -hour reduction in eating window) (TRE) for 3 months. Timing of dietary intake was tracked in real-time using the myCircadianClock smartphone application.

Measurements.

Primary outcomes: HbA1c, fasting glucose, fasting insulin, HOMA-IR, and glycemic assessments from continuous glucose monitors (CGM).

Results.

108 participants completed the intervention (89% of randomized, 56 females; mean baseline age of 59 years, BMI of 31.22 kg/m², eating window of 14.19 hours). TRE improved HbA1c by -0.10% (95% CI: -0.19 to -0.003). Statistical outcomes were adjusted for age. There were no major adverse events.

Limitations.

Short duration, self-reported diet, potential for multiple elements affecting outcomes.

Conclusion.

Personalized 8–10 h TRE is an effective practical lifestyle intervention that modestly improves glycemic regulation and may have broader benefits for cardiometabolic health in adults with MetS on top of standard-of-care pharmacotherapy and nutritional counseling.

Primary Funding Source.

NIH

Introduction

Metabolic syndrome (MetS) is a progressive pathophysiological state, affecting over one-third of the US population and over one billion people worldwide. MetS with prediabetes represents a critical tipping point that increases the risk of developing Type II Diabetes Mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) making it an important target for primary prevention ([1](#)). There is an unmet need for evidence-based lifestyle interventions to attenuate the progression of prediabetes to diabetes and decrease the burden of cardiometabolic disease. Time-restricted eating (TRE) is a promising lifestyle intervention with strong evidence in animal and/or mechanistic studies that address multiple aspects of metabolic syndrome. TRE optimizes circadian physiology by restricting daily food intake to a consistent 8–10 hour window, without overtly mandating calorie restriction (CR); although inadvertent CR may occur ([2](#)).

Previous clinical results assessing the cardiometabolic benefits of TRE are mixed. In studies involving a reduction of ≥ 4 h of eating window from baseline and/or an eating window of ≤ 10 h, TRE has demonstrated a variety of cardiometabolic benefits including improved glycemic control ([3](#)), decreased blood pressure ([4–6](#)), weight loss ([3, 7–9](#)), and improved atherogenic lipid profiles ([4, 10, 11](#)). Other studies have shown no benefit of TRE ([12, 13](#)). Some common features of these negative trials are that they examined individuals who had obesity without underlying cardiometabolic abnormalities and/or already had a short (≤ 10 h) eating window, or the study lacked sufficient participant engagement and adherence monitoring. TRE appears to be most beneficial when people with cardiometabolic derangements and a relatively longer eating window are guided to reduce their eating window by ≥ 4 h. In a pilot study in participants with metabolic syndrome, TRE decreased weight, body fat, and total cholesterol, but did not significantly improve glycemic parameters. However, the primary outcome was not glycemic control, and elevated HbA1c was not a criterion for participation.

This randomized control trial (RCT) is unique as it assesses the efficacy of personalized 8–10 h TRE in adults with metabolic syndrome including prediabetes on top of the patient’s current standard of care including pharmacotherapy. As is customary to assess safety and feasibility before a long-term study, this RCT tested the effects of 3 months of TRE compared to standard-of-care (SOC).

Methods

Design Overview

The TIMET study was a 1:1 randomized controlled trial, mixed design, with two groups (TRE and SOC) assessed at two time points (baseline and end of the 3-month intervention). Participants were recruited from April 29, 2019, through October 24, 2022, and final visits were completed on January 19, 2023. The study was approved by the institutional review boards at the University of California, San Diego (IRB# 181088) and the Salk Institute for Biological Studies (IRB# 18–0011), and registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04057339) ([NCT04057339](https://clinicaltrials.gov/ct2/show/study/NCT04057339)). See [Supplemental Protocol](#) for more details.

Setting and Participants

All clinic visits were held at The University of California, San Diego Altman Clinic for Translational Research Institute in La Jolla, California.

Participants were recruited through flyers, online advertisements, and messages sent to potential participants screened through electronic health records at UCSD Health.

Adults (18–75 years) were eligible if they had an elevated BMI (≥ 25 kg/m² and ≤ 41 kg/m²), metabolic syndrome, and elevated fasting glucose characteristic of prediabetes (between 100–125 mg/dL) or HbA1c (between 5.7%–7.0%). Medications including statins and other lipid-modifying drugs, anti-hypertensives, and anti-diabetes drugs were allowed. Exclusion criteria included an unstable medication regimen (changing medications/doses, or weight loss medications/plans in the past 3 months), pregnant/breastfeeding, or sleep disruption from shift work or care responsibilities (see the [Supplemental Protocol](#) for full inclusion/exclusion and eligibility changes).

Randomization and Intervention

The study statistician generated a randomization table with SPSS using block sizes of 4 and 6 and informed the study coordinators of the randomization group after participants were successfully screened.

At clinic visit one (CV1), consent was obtained, and baseline/screening assessments were conducted, including fasting blood draw, blood pressure, height, weight, waist circumference, and questionnaires. All participants completed two-week electronic logs of the timing of dietary intake in the myCircadianClock (mCC) app and wore a continuous glucose monitor (CGM, Abbott Freestyle Libre Pro) and an actigraphy device (Phillips Respironics Actiwatch Spectrum Plus, Cat#1104775). At CV2, eligible participants completed additional baseline assessments (Dual-energy X-ray absorptiometry (DXA) and a 24-hour dietary recall), received nutritional counseling from a registered dietitian, and were randomized to either the TRE or SOC group. No instructions were given to participants in either group on changing energy intake.

The SOC group was advised to continue their habitual eating patterns. As is a standard of care for MetS patients in a primary care clinic, they were advised to follow a healthy lifestyle including nutritional advice such as a Mediterranean diet ([14](#)), one of the dietary recommendations of the American Heart Association.

The TRE group received the same lifestyle and nutritional recommendations and in addition, were assigned a personalized 8–10 h eating window. Personalization of the TRE eating window was (a) based on the participant's baseline eating window and (b) scheduled relative to their habitual sleep time (ended ≥ 3 h before habitual bedtime). A target eating window of 8–10 h was achieved by ≥ 4 h reduction in the eating window relative to baseline (ex: 13 h would decrease to 9 h). Participants with an eating window ≥ 14 h at baseline were assigned a 10 h eating window. Only water and prescribed medications were allowed outside the eating window.

All participants followed the intervention for 3 months during which they logged the timing of dietary intake in the mCC app every day. After 6 weeks, all participants had a second 24-hour dietary recall and phone discussion with a registered dietitian about their diet. Two weeks before the intervention concluded, participants returned

for CV3, to receive a CGM and actiwatch. At the end of the intervention, participants returned for CV4, repeating all baseline assessments including the 3rd and final meeting with the dietician ([Figure 1](#)).

Figure 1. Consort Diagram and Study Timeline.



[Open in a new tab](#)

(A) Timeline of study visits and assessments. (B) Consort diagram of participants from screening through completion of the intervention. CV = clinic visit, mCC = myCircadianClock, CGM = continuous glucose monitor, DXA = dual-energy X-ray absorptiometry, TRE = time-restricted eating, SOC = standard-of-care.

Intervention delivery:

Except for the consultation with the registered dietician, all guidance for intervention was delivered through the mCC app. Participants in each group received 98 daily pre-scheduled messages (14 during baseline and 84 during intervention) including 36 blogs (3/week) during the 3-month intervention period. Content of the messages and blogs included guidance on physical activity, restful sleep, stress reduction, healthy diet, and

prompts to record dietary timing with specific modifications for each group where applicable. At least 3 days a week, the research team remotely monitored participants' food logs on the app dashboard to ensure adherence to logging of food timing.

Outcomes and Follow-up

The primary outcomes were (1) HbA1c and (2) additional glycemic parameters including fasting blood glucose, fasting insulin, HOMA-IR (fasting insulin*fasting glucose/405) ([15](#)), and glycemic assessments via CGM. CGM data were analyzed using the R package rGV ([16](#)). From the CGM data, we assessed mean glucose (mg/dL), intra-glycemic variability with CONGA (Continuous Overall Net Glycemic Action), and inter-glycemic variability with MODD (Mean of Daily Differences). CONGA assesses the standard deviation of differences between glucose values measured at regular time intervals ([17](#)). MODD takes the mean of absolute differences between glucose values at a given time, with the same time the previous day ([18](#)).

The original primary outcome was changes in fasting glucose, and HbA1c was among the secondary outcomes. On December 2, 2021, the primary outcomes were updated in the IRB to be HbA1c and other glycemic parameters (listed above) as HbA1c is a more accurate measure of glycemic control as fasting glucose can vary greatly within and between days ([Supplemental Protocol](#)). No data analysis was run before this change.

Secondary outcomes were cardiometabolic parameters including LDL particle number (assessed via NMR Lipoprotein Profile), direct LDL-cholesterol, HDL-cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), and trunk fat mass assessed by DXA (Hologic, Discovery W densitometer, S/N: 301720M, Waltham, MA, USA), analyzed with Hologic, APEX 13.6.0.7. Exploratory outcomes include weight, BMI, blood pressure, and body composition assessed via DXA (% body fat, total lean mass, and total bone mineral content (BMC)). All blood samples were collected between 7–11 am in a fasted state (≥ 12 h).

Eating window and adherence to TRE were assessed with the mCC app ([19](#)). The eating window was calculated as the mid 95%ile time window of all caloric entries within two weeks. This calculation accounts for the inter-daily variability in the timing of dietary intake ([4](#), [11](#), [20](#)).

Wrist-worn actigraphy was used to assess changes in activity and sleep. Questionnaires were used to assess subjective sleep (Pittsburg Sleep Quality Index, PSQI ([21](#)); and Epworth Sleepiness Scale, ESS), quality of life (36 Item Short-Form Health Survey, SF-36), and depression, (Beckman Depression Index-II, BDI-II). 24-hour dietary recalls were used to estimate changes in calorie intake between baseline and intervention.

All outcomes were assessed at baseline (V1 or V2) and the end of the 3-month intervention (V4) ([Figure 1A](#)).

Statistical Analysis

The required sample size was calculated using G*Power software and for the mixed model approach using the RMASS program provided by Hedeker (<http://tigger.uic.edu/~hedeker/ml.html> [↗](#)). The sample size was chosen

to provide a minimum power of 80% to detect a medium effect size of 0.55 for HbA1c (approximately 0.1%). Effects sizes (Cohen's D) were determined for fasting and HbA1c glucose from participants who had elevated glucose from our pilot study (4). While a decrease of 0.5% in HbA1c is generally considered clinically important in patients with Type 2 Diabetes, in our population of patients with prediabetes, a decrease of 0.1% is considered clinically meaningful (23).

All participant data were used for statistical analysis when both baseline and end-of-intervention data were obtained. Data was initially examined using descriptive statistics and exploratory graphing to assess the normality and homogeneity of the data. The two groups were compared on baseline demographic and clinical features using independent t-tests. Missing data from participants who withdrew from the study were examined for randomness using independent t-tests to compare all withdrawals from all completers (Supplemental Table 1). Reasons for all missing data are listed in Supplemental Table 2. Study outcomes were assessed with two-factor (intervention group by time) Repeated Measures Mixed-ANOVA and were adjusted for age. All statistical tests were two-tailed. Data are reported as mean (SD) for normally distributed data and mean (95% CI) for delta values. For primary outcomes, differences were considered statistically significant provided a p-value of 0.05 or less. Data analysis was performed using the R package rGV (16) and SPSS version 28. The full statistical plan is provided in the Supplemental Protocol.

Role of the Funding Source

The funders had no role in the study design, data collection, statistical analysis, manuscript preparation, or publication.

Results

Study population

From April 29, 2019, through October 24, 2022, 122 participants were randomized (TRE/SOC: 61/61). 108 of the 122 participants (89%, 54 per group) completed the 3-month intervention (Figure 1B). Baseline characteristics were comparable between groups; however, we were not powered to detect differences in all baseline characteristics such as in race/ethnicity. Statistics were adjusted for age as it was the most notable difference, with a mean age 56.78 y (SD: 11.34 y) in TRE and 61.43 y (9.17 y) in SOC (Table 1). Baseline levels of glycemic regulation were all comparable between groups with mean HbA1c of 5.87% (0.34%) in TRE and 5.86% (0.27%) in SOC (Table 2). Medications were similar between groups with 6% of participants taking metformin for prediabetes, 48% for hyperlipidemia, and 69% taking ≥ 1 medication for cardiometabolic health which includes antihypertensives. The TRE group had more participants on at least 1 medication for metabolic syndrome, and the SOC group had more participants on multiple medications (Table 1).

Table 1.

Baseline Characteristics

<u>Demographics</u>	<u>TRE</u> (n=61)	<u>SOC</u> (n=61)
Age, years [*]	56.6 (11.5)	60.6 (10.3)
Male, n (%)	30 (49)	30 (49)
Female, n (%)	31 (51)	31 (51)
White, n (Hispanic or Latino, n)	36 (1)	38 (2)
Black, n (Hispanic or Latino, n)	7 (0)	2 (0)
Asian, n (Hispanic or Latino, n)	10 (0)	16 (0)
Native Hawaiian or Other Pacific Islander, n (Hispanic or Latino, n)	2 (0)	0
Mixed Race, n (Hispanic or Latino)	4 (2)	5 (3)
Declined to disclose race/ethnicity, n	2	0
<u>Medications for Treatment of Metabolic Syndrome</u>		
Metformin, n (%)	4 (7)	3 (5)
Statins, n (%)	29 (48)	31 (52)
Anti-Hypertensives and Diuretics, n (%)	28 (46)	31 (52)
Non-statin lipid-lowering drugs, n (%)	2 (3)	2 (3)
1 or more medication listed above, n (%)	46 (75)	38 (62)
<u>Metabolic Syndrome Classification</u>		
HbA1c $\geq$ 5.7 %, Fasting Glucose $\geq$ 5.55 mmol/L (100 mg/dL) or drug treatment, n (%)	61 (100)	61 (100)
HDL cholesterol: M < 1.03 mmol/L (40 mg/dL) or F < 1.29 mmol/L (50 mg/dL) (F), or drug treatment for reduced HDL-cholesterol, n (%)	44 (73)	42 (69)
Triglycerides $\geq$ 1.69 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides, n (%)	25 (41)	25 (41)
SBP $\geq$ 130 mmHg and/or DBP $\geq$ 85 mmHg, or Drug Treatment for Hypertension, n (%)	48 (79)	44 (73)
Waist Circumference: Asian: $\geq$ 90 cm (M) or $\geq$ 80 cm (F); all other races: $\geq$ 102 cm (M) or $\geq$ 88 cm (F), n (%)	52 (85)	55 (90)

Baseline characteristics for all randomized participants (n=122). All data are presented as mean (SD) unless otherwise specified. Independent T-tests were used to assess differences between groups, with p-value <0.05 considered significant (*). Only age was significantly different between TRE and SOC at baseline (p=0.044). Non-statin lipid-lowering drugs include fenofibrate, icosapent ethyl, ezetimibe, and omega-3 fatty acid ethyl ester. TRE = time-restricted feeding, SOC = standard of care, HbA1c = hemoglobin A1c (glycated hemoglobin), SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table 2.

Primary Outcomes: Glucose Regulation

Outcomes	TRE				SOC				Betw
	Baseline	3- Month	Delta (95% CI)	Percent Change	Baseline	3- Month	Delta (95% CI)	Percent Change	Del TR SO
HbA1c, %	5.87 (0.34)	5.75 (0.31)	−0.12 (−0.19 to −0.05)	−2.0%	5.86 (0.27)	5.84 (0.29)	−0.02 (−0.09 to 0.04)	−0.3%	−0.02 (−0.09 to −0.05)
Fasting Glucose									
mmol/L	5.76 (0.57)	5.49 (0.52)	−0.27 (−0.42 to 0.12)	−4.7%	5.82 (−0.67)	5.73 (−0.62)	−0.08 (−0.25 to 0.09)	−1.4%	−0.09 (−0.25 to 0.07)
mg/dL	103.78 (10.20)	98.94 (9.30)	−4.83 (−7.48 to −2.19)		104.83 (12.02)	103.33 (11.25)	−1.50 (−4.54 to 1.54)		−3.40 (−7.48 to 0.68)
Fasting Insulin									
pmol/L	124.18 (96.05)	104.24 (58.06)	−20.00 (−44.38 to 4.44)	−16.1%	117.37 (57.64)	109.04 (69.10)	−8.40 (−24.10 to 7.36)	−7.2%	−11.33 (−40.67 to 17.99)
mlU/L	17.88 (13.83)	15.01 (8.36)	−2.88 (−6.39 to 0.64)		16.90 (8.30)	15.70 (9.95)	−1.21 (−3.47 to 1.06)		−1.19 (−5.11 to 2.72)
HOMA- IR, A.U.	4.61 (3.51)	3.72 (2.24)	−0.89 (−1.93 to 0.05)	−19.3	4.44 (2.48)	4.06 (2.65)	−0.38 (−1.07 to 0.31)	−8.6%	−0.38 (−1.07 to 0.31)
CGM Mean Glucose (mmol/L)									
mmol/L	5.64 (0.51)	5.52 (0.62)	−0.13 (−0.29 to 0.04)	−2.2%	5.65 (0.63)	5.76 (0.58)	0.11 (−0.07 to 0.29)	+1.9%	0.11 (−0.07 to 0.29)
mg/dL	101.68 (9.19)	99.41 (11.24)	−2.26 (−5.27		101.81 (11.36)	103.79 (10.50)	1.98 (−1.33		−4.97 (−8.98

Outcomes	TRE				SOC				Betw
	Baseline	3- Month	Delta (95% CI)	Percent Change	Baseline	3- Month	Delta (95% CI)	Percent Change	Del TR SO
CGM CONGA, A.U.	19.96 (4.34)	18.49 (4.67)	to 0.75)	−7.4%	18.89 (4.51)	18.95 (4.85)	to 5.30)	+0.3%	to 0.
			−1.47 (−2.53 to −0.41)				0.06 (−0.99 to 1.11)		−1. (−3 to −0.1)
			CGM MODD						
mmol/L	0.98 (0.29)	0.86 (0.24)	−0.10 (−0.16 to 0.05)	−10.8%	0.89 (0.20)	0.92 (0.26)	0.03 (−0.03 to 0.09)	+3.3%	−0. (−0 to −0.1)
mg/dL	17.71 (5.31)	15.56 (4.40)	−1.89 (−2.89 to 0.88)		16.03 (3.60)	16.56 (4.77)	0.53 (−0.58 to 1.64)		−2. (−3 to −0.1)

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Data displayed as Mean (SD) and Mean (95% Confidence Interval) for delta values. Paired t-tests were used to assess within-group changes and Mixed ANOVAs were used to assess changes between TRE and SOC (time x group) with age as a covariate. N=54 per group for all outcomes except for the CGM measurements: TRE n=52, SOC n= 53. There was no pattern of missingness between groups ([Supplemental Table 2](#)). TRE = time-restricted eating, SOC = standard of care, HbA1c = hemoglobin A1c (glycated hemoglobin), HOMA-IR = homeostasis model assessment of insulin resistance, CGM = continuous glucose monitor, GMI = glucose management indicator (short-term CGM estimate of HbA1c), CONGA = continuous overall net glycemic action, A.U. = arbitrary units, MODD = mean of daily differences.

Glycemic Parameters

The primary glycemic outcome of HbA1c decreased to a greater degree in the TRE group compared to SOC; the net between group difference was -0.10% (95% CI -0.19, -0.003%), a -1.7% relative reduction ([Table 2](#)). There were no differences in outcomes when participants taking metformin were removed from the analysis (3 per group) ([Supplemental Table 3](#)). Changes in HbA1c had very weak correlations with changes in weight loss (TRE, $R^2 = 0.07$, SOC, $R^2 = 0.03$) and kilocalories (TRE, $R^2 = 0.02$, SOC, $R^2 = 0.01$) ([Supplemental Figure 1](#)).

While participants in the TRE also had a numerically greater decrease in fasting glucose, fasting insulin, HOMA-IR and CGM mean glucose, estimates were imprecise and included the null ([Table 2](#)). In addition, compared to SOC, TRE decreased both intra-daily glycemic variations assessed by CONGA (Continuous Overall Net Glycemic Action) and inter-daily glycemic variation assessed via MODD (Mean of Daily Differences) ([Table 2](#)).

Cardiometabolic Risk Factors

Secondary and exploratory outcomes in body composition and cardiometabolic risk factors were consistent with the benefits seen in glucose regulation and tended to favor TRE ([Table 3](#)).

Table 3.

Secondary and Exploratory Outcomes: Cardiometabolic Outcomes

Outcomes	TRE				SOC		
	Baseline	3-Month	Delta (95% CI)	Percent Change	Baseline	3-Month	Delta (95% CI)
<u>Body Composition</u>							
Weight, kg	89.94 (16.98)	86.96 (17.06)	−2.98 (−4.11 to −1.84)	−3.3%	89.25 (16.48)	87.93 (16.23)	−1.32 (−2.07 to −0.57)
BMI, kg/m ²	31.50 (4.06)	30.38 (4.37)	−1.11 (−1.51 to −0.72)	−3.5%	30.95 (4.03)	30.55 (4.11)	−0.39 (−0.66 to −0.13)
Percent Body Fat, %	37.70 (6.90)	36.34 (7.35)	−1.36 (−2.00 to −0.73)	−3.6%	38.62 (6.62)	38.51 (6.81)	−0.11 (−0.71 to 0.49)
Trunk Fat ^, %	39.43 (5.88)	37.88 (6.50)	−1.55 (−7.87 to −0.90)	−3.9%	40.33 (5.99)	40.18 (6.20)	−0.15 (−0.83 to 0.53)
Total Fat Mass, g	33263.73 (8306.52)	31023.51 (8490.32)	−2240.22 (−3044.43 to 1376.01)	−6.7%	33572.58 (7634.67)	33163.47 (8027.05)	−409.11 (−1093.1 to 273.89)
Total Lean Mass, g	52504.06 (11954.31)	52228.52 (12246.54)	−275.53 (−773.69 to 222.62)	−0.5%	51544.89 (12182.13)	50977.86 (11991.96)	−567.03 (−1107.9 to −26.11)
Total BMC, g	2458.77 (543.28)	2462.99 (551.40)	4.22 (−11.54 to 19.98)	0.0%	2439.74 (548.23)	2442.64 (567.37)	2.89 (−13.55 to 19.34)
<u>Cardiometabolic Parameters</u>							
LDL Direct Cholesterol ^							
mmol/L	3.12 (1.07)	2.84 (1.03)	−0.27 (−0.41 to −0.13)	−8.7%	3.02 (0.92)	2.98 (1.07)	−0.04 (−0.16 to 0.09)

Outcomes	TRE					SOC		
	Baseline	3-Month	Delta (95% CI)	Percent Change		Baseline	3-Month	Delta (95% CI)
mg/dL	120.48 (41.47)	110.00 (39.95)	−10.48 (−15.83 to −5.13)	−8.2%	116.78 (35.62)	115.41 (41.44)	−1.37 (−6.38 to 3.64)	
LDL particle number, nmol/L	1527.87 (485.45)	1402.40 (490.54)	−125.46 (−191.90 to −59.03)		1533.25 (423.01)	1485.25 (445.25)	−48.00 (−104.64 to 8.64)	
HDL Cholesterol ^								
mmol/L	1.36 (0.40)	1.33 (0.35)	−0.04 (−0.07 to 0.00)	−2.6%	1.39 (0.41)	1.39 (0.38)	−0.01 (−0.05 to 0.03)	
mg/dL	52.70 (15.43)	51.33 (13.62)	−1.37 (−2.90 to 0.15)		53.94 (16.01)	53.57 (14.85)	−0.37 (−1.98 to 1.24)	
Triglycerides ^								
mmol/L	1.66 (0.72)	1.57 (0.76)	−0.09 (−0.22 to 0.05)	−5.3%	1.73 (0.87)	1.57 (0.65)	−0.16 (−0.30 to 0.02)	
mg/dL	146.81 (63.49)	139.04 (67.19)	−7.78 (−19.78 to 4.23)		152.87 (76.78)	138.93 (57.34)	−13.94 (−26.17 to −1.82)	
hs-CRP ^, mg/L	2.44 (2.65)	2.25 (2.53)	−0.19 (−0.66 to 0.28)		−7.8%	2.63 (2.78)	2.54 (3.13)	−0.09 (−0.89 to 0.71)
SBP, mm/Hg	131.76 (15.22)	128.28 (12.27)	−3.48 (−7.87 to 0.91)	−2.6%	127.89 (13.96)	126.17 (13.84)	−1.72 (−5.91 to 2.47)	
DBP, mm/Hg	75.65 (10.93)	71.67 (10.23)	−3.98 (−7.06 to −0.90)	−5.3%	74.88 (11.79)	73.44 (10.97)	−1.44 (−3.81 to 0.93)	

Data displayed as Mean (SD) and Mean (95% Confidence Interval) for delta values. Paired t-tests were used to assess within-group changes and Mixed ANOVAs were used to assess changes between TRE and SOC (time x group) with age as a covariate. Body Composition was assessed via DXA body scan. N=54 per group for all outcomes except for the following: DXA measurements: SOC n=52; LDL particle number, n=52 per group (missing data due to lab error: interference); hs-CRP: TRE n=53. There was no pattern of missingness between groups ([Supplemental Table 2](#)). TRE = time-restricted eating, SOC = standard of care, BMI = body mass index, BMC = bone mineral content, LDL = low-density lipoprotein, HDL = high-density lipoprotein, hs-CRP = high sensitivity C-reactive protein, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Compared to SOC, TRE had greater reductions in body weight, BMI, percent body fat, total fat mass, and percent trunk fat ([Table 3](#)). Importantly, we did not observe a greater decrease in lean mass in the TRE vs the SOC group ([Table 3](#), [Supplemental Table 4](#)).

[Table 3](#), [Supplemental Table 5](#) presents the effect TRE vs SOC on lipids levels, hs-CRP, and systolic and diastolic blood pressure. LDL cholesterol decreased in TRE compared to SOC. Other estimates were imprecise though tended to favor TRE.

When assessing metabolic syndrome factors based on health factors alone (i.e. not counting taking medication for a condition), 61% (33/54) of TRE participants and 54% (29/54) of SOC participants decreased at least one factor used qualifying metabolic syndrome factors (HbA1c, fasting glucose, SBP, DBP, waist circumference, BMI, HDL, or TG) ([Supplemental Tables 6](#)). In both groups, there was a similar decrease in the number of participants that qualified for metabolic syndrome at the end of intervention compared to baseline (−23% TRE and −22% SOC) ([Supplemental Figure 2](#) and [Supplemental Table 7](#)).

Change in Eating Window and Adherence to Intervention

Participants logged the timing of 9,682 and 45,432 calorie-containing dietary logs during the 2-weeks of baseline and the 3-month intervention respectively ([Table 4](#)). Both groups had an average eating window of ≥ 14 h at baseline ([Table 4](#)). TRE participants decreased their eating window by −4.55 h (−5.06 to −4.04 h) compared to baseline, and by −4.30 h (−4.97 to −3.64 h) compared to SOC. At the end of the intervention, the average eating window in the TRE group started at 9:14 am and ended at 6:59 pm ([Supplemental Table 8](#)). 11.6% (13.9%) of days had a caloric entry consumed more than 15 mins outside their personalized eating window throughout the intervention, indicating adherence to TRE eating window >85% ([Table 4](#)).

Table 4.

Eating Window and Adherence

Study Phase	TRE (n=54)			SOC (n=54)		
	Baseline	Intervention (Last 2 weeks)	Intervention (Full 3 months)	Baseline	Intervention (Last 2 weeks)	Intervention (Full 3 months)
Duration (days)	14	14	91.04 (1.62)	14	14	89.26 (1.24)
Number of caloric entries	4,635	3,479	23,118	5,047	3,463	22,314
95% eating window (hours)	14.38 (1.72)	9.83 (1.43)	10.09 (1.47)	14.00 (1.38)	13.75 (1.57)	14.17 (1.40)
Change in eating window (hours)	-	-4.55 (-5.06 to -4.04)	-4.29 (-4.79 to -3.80)	-	-0.25 (-0.68 to 0.19)	0.17 (-0.22 to 0.56)
Percent of days outside the eating window	-	10.6% (13.8%)	11.6 % (13.9%)	-	-	-

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Data is shown as mean (SD) for each time point and mean (95% CI) for changes between time points. The data shown is based on entries on the myCircadianClock app. TRE= time-restricted eating, SOC = standard of care.

TRE participants increased the time between wake and eating window start by 1 h 49 m (1h 5m) and eating window end and bedtime by 2h 50m (1h 40m). There was no change in the eating window relative to bedtime or wake time in the SOC group ([Supplemental Figure 3](#), [Supplemental Table 8](#)).

Sleep and quality of life

There was no appreciable change in bedtime, wake time, sleep duration or physical activity between baseline and intervention in either group ([Supplemental Tables 8–10](#), [Supplemental Information 1](#)). There were no other notable changes in self-reported sleep (PSQI and ESS) and quality of life (SF-36) or depression (BDI-II) ([Supplemental Table 9](#)). There was no pattern of missingness in incomplete actiwatch and/or PSQI data from participants that completed the study ([Supplemental Table 2](#)).

Energy Intake and Macronutrients

The TRE group reduced energy intake by an average of 350 Kcal, based on 24-h dietary recall. The reduction in calorie intake was largely accounted for by the reduction in carbohydrates and dietary fat and no substantial reduction in dietary protein ([Supplemental Table 11](#)).

Adverse Event

One participant in TRE reported irritability, fatigue, and difficulty concentrating on a 10-hour TRE schedule (9:30 a.m. to 7:30 p.m.). No other adverse events were reported.

Discussion

In this RCT of adults with metabolic syndrome, including prediabetes on standard-of-care medical therapy, we found that personalized 8–10 h TRE improved glycemic regulation compared to SOC, with no major adverse events. HbA1c and glycemic variability, assessed via CGM, showed the largest changes between groups. Other measures of glycemic regulation and cardiometabolic risk factors (body composition and plasma biomarkers) were also generally more favorable with TRE.

In this population with an average baseline HbA1C of 5.87% (0.33%), 3 months of TRE, on top of current treatment, including medication and diet, decreased HbA1c compared to SOC by -0.10% . Prior seminal clinical trials such as the Diabetes Prevention Program (DPP) have shown that a decrease in HbA1C of 0.1 among individuals with prediabetes reduces future incidence of T2DM. The 3,234 participants in the DPP had a comparable baseline HbA1c of 5.91% (0.50%). The intensive lifestyle intervention arm of DPP -- which consisted of 24 weeks of personalized reduction in energy intake and $\sim 50\%$ increase in weekly physical activity ([22](#)) -- resulted in a reduction in HbA1c by 0.1%, and a reduction in the incidence of T2DM by 58% at the 2.8-year follow-up ([23](#)). In the same study, Metformin 850mg twice daily combined with standard lifestyle advice achieved $<0.07\%$ reduction in HbA1C and 31% reduction in the incidence of T2DM. In this study, the intervention was implemented through the mCC app which facilitated personalized eating windows and comprehensive real-time logging/monitoring via a smartphone app to assess adherence. The mCC app also enables future studies to be remote and/or at a much larger scale.

Consistent with the decrease in HbA1c, TRE also improved additional measures of glycemic control assessed by CGM including inter- and intra-daily glycemic variability (GV; CONGA and MODD, respectively). GV represents the fluctuations of glucose across a 24-h day. Elevated GV is associated with increased risk for T2DM and adverse

cardiometabolic outcomes (24). GV increases in adults with prediabetes compared to healthy controls (25) and is a key component of T2DM dysglycemia (26). Therefore, the decreased GV in TRE compared to SOC, may have implications for improved long-term cardiometabolic health outcomes beyond decreased HbA1c.

We also saw greater decreases in weight (−3.3%), BMI (−3.5%), and trunk fat (−3.9%) with TRE that are consistent with other studies assessing TRE for weight loss (4, 11, 27). This weight loss may be in part due to a decrease in calories intake assessed via 24-hour dietary recall (Supplemental table 11), similar to TRE studies with no over restriction on calorie intake. There was no change in physical activity (Supplemental table 10). Importantly, of the average weight loss of 2.98 kg in the TRE group, 2.24 kg (approximately 75%) was due to loss of fat mass and only 0.28 kg (~9%) was from lean mass, a more favorable profile than with SOC. This suggests that TRE likely poses a lower risk for sarcopenia associated with weight loss. Our findings contrast with a TRE intervention in which the TRE group lost disproportionately more body weight from lean mass due to inadvertently reducing physical activity by as much as 25% (12). Additional studies are needed to confirm this and other secondary outcome findings in our study.

A limitation of this study is that the study lasted for 3 months. Longer and larger trials lasting a year or more (such as the DPP) are needed to understand the sustainability and long-term effects of TRE in reducing cardiometabolic disease risk factors. The study also lacked an active control arm to compare treatments. Finally, there may be multiple elements contributing to health outcomes such as biological sex and changes in adiposity. Although we adjusted for age (the only baseline factor different between groups), the study was not adequately powered to adjust for other factors.

In conclusion, TRE is an effective lifestyle strategy that can be used concomitantly with the current standard of care pharmacotherapies and nutritional counseling, to further improve glycemic regulation, and potentially multiple components of cardiometabolic health, in patients with metabolic syndrome.

Supplementary Material

study protocol

[NIHMS2059427-supplement-study_protocol.pdf](#) (1.3MB, pdf)

Supplementary

[NIHMS2059427-supplement-Supplementary.docx](#) (325.3KB, docx)

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Footnotes

IRB Approval. The study was approved by the institutional review boards at the University of California, San Diego (IRB# 181088) and the Salk Institute for Biological Studies (IRB# 18–0011).

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Associated Data

This section collects any data citations, data availability statements, or supplementary materials included in this article.

Supplementary Materials

study protocol

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Supplementary

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