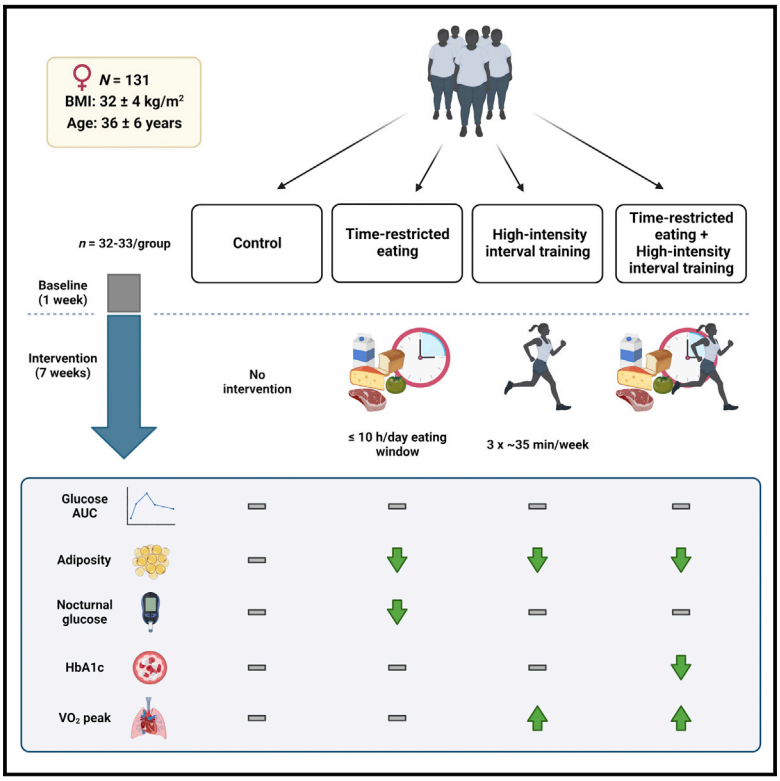
Cell Metabolism
Clinical and Translational Report

Time-restricted eating and exercise training improve HbA1c and body composition in women with overweight/obesity: A randomized controlled trial

Graphical abstract



Highlights

- Time-restricted eating (TRE) reduces nocturnal glucose in women with overweight/obesity
- TRE combined with high-intensity interval training (HIIT) decreases HbA1c
- The combination of TRE and HIIT reduces visceral fat more than TRE and HIIT alone
- TRE and HIIT are feasible strategies to improve metabolic health in this population

Authors

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In brief

Time-restricted eating (TRE) and high-intensity interval training (HIIT) can improve cardiometabolic health, but whether combining these interventions induces superior metabolic improvements over each intervention alone is not known. In a randomized controlled trial, women with overweight/obesity completed 7 weeks of TRE, HIIT, or a combination (TREHIIT). Haganes et al. report that TRE, HIIT, and TREHIIT reduced visceral fat, while the combination of TRE + HIIT also improved HbA1c. TREHIIT was found to be feasible for women with overweight/obesity for the 7-week period.

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Time-restricted eating and exercise training improve HbA1c and body composition in women with overweight/obesity: A randomized controlled trial

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SUMMARY

Diet modification and exercise training are primary lifestyle strategies for obesity management, but poor adherence rates limit their effectiveness. Time-restricted eating (TRE) and high-intensity interval training (HIIT) improve cardiometabolic health in at-risk individuals, but whether these two interventions combined induce superior improvements in glycemic control than each individual intervention is not known. In this four-armed randomized controlled trial (ClinicalTrials.gov NCT04019860), we determined the isolated and combined effects of 7 weeks of TRE (≤10-h daily eating window, with *ad libitum* energy intake) and HIIT (three exercise sessions per week), compared with a non-intervention control group, on glycemic control and secondary cardiometabolic outcomes in 131 women (36.2 ± 6.2 years) with overweight/obesity. There were no statistically significant effects after isolated TRE, HIIT, or a combination (TREHIIT) on glucose area under the curve during an oral glucose tolerance test (the primary outcome) compared with the control group (TRE, −26.3 mmol/L; 95% confidence interval [CI], −82.3 to 29.7, p = 0.36; HIIT, −53.8 mmol/L; 95% CI, −109.2 to 1.6, p = 0.057; TREHIIT, −41.3 mmol/L; 95% CI, −96.4 to 13.8, p = 0.14). However, TREHIIT improved HbA1c and induced superior reductions in total and visceral fat mass compared with TRE and HIIT alone. High participant adherence rates suggest that TRE, HIIT, and a combination thereof may be realistic diet-exercise strategies for improving markers of metabolic health in women at risk of cardiometabolic disease.

INTRODUCTION

Reproductive-aged women with obesity and insulin resistance have increased risk of type 2 diabetes mellitus and cardiovascular disease, and are also predisposed to adverse pregnancy outcomes, including adiposity and cardiometabolic disorders in their offspring (Catalano and Shankar, 2017). While a healthy diet and regular physical activity are primary lifestyle strategies for the prevention and treatment of obesity and its associated conditions, poor adherence rates limit their effectiveness. Time-restricted eating (TRE) is a popular dietary strategy that emphasizes the timing of meals in alignment with diurnal circadian rhythms, permitting *ad libitum* energy intake during a restricted eating window (~8–10 h between the first and last energy intake of the day) (Gill and Panda, 2015). Unlike other dietary approaches that modify the feeding-fasting cycle (i.e., chronic energy restriction or intermittent fasting), TRE is a chrono-nutritional strategy in which the timing of meals is closely aligned with typical metabolite and hormonal profiles over 24-h periods (Asher and Sassone-Corsi, 2015; Hawley et al., 2020). While TRE places no restrictions on total energy intake or the macronutrient composition of food, individuals often spontaneously reduce their energy intake, inducing a mild (1%–4%) body weight loss over intervention periods lasting from 1 week to 3 months (Kang et al., 2021). TRE also improves insulin sensitivity without weight loss in men with overweight and prediabetes (Sutton et al., 2018) and in healthy individuals without obesity (Xie et al., 2022). High-intensity interval training (HIIT) performed as short, repeated bouts of high-intensity aerobic exercise separated by low-intensity breaks, is a time-efficient alternative to the current higher-volume physical activity recommendations and improves cardiorespiratory fitness and insulin sensitivity in high-risk populations (Mattioni Maturana et al., 2021).

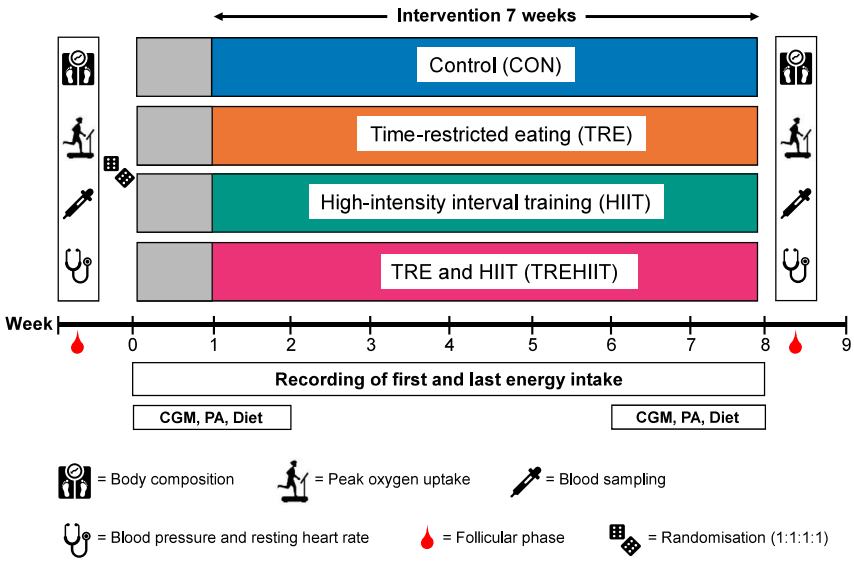

Figure 1. Study design

Participants visited the laboratory for assessments on two separate days prior to randomization and again after the intervention. Assessments were identical at pre- and post-intervention. One of the test days included fasting blood samples, an oral glucose tolerance test, body composition analysis, blood pressure and resting heart rate measurements, and three questionnaires: International Physical Activity Questionnaire, Pittsburgh Sleep Quality Index, and Horne-Ostberg Morningness-Eveningness Questionnaire. The other test day consisted of a cardiorespiratory fitness test to determine peak oxygen uptake (VO_2peak) and maximal heart rate (HR_{max}). After completed pre-assessments, participants were randomized to one of the four study groups. Participants were fitted with continuous glucose monitors (CGMs) and physical activity monitors (PA) and reported diet and appetite for the first and last 14 days of the study. All laboratory assessments were conducted during the follicular phase in women with a regular menstrual cycle. Time points of first and last energy intake were reported every day throughout the study.

Despite the substantially lower exercise time, HIIT is as effective for weight loss as prolonged, continuous moderate-intensity exercise for obesity treatment (Mattioni Maturana et al., 2021). Both HIIT and TRE hold promise as practical diet-exercise strategies to improve metabolic health in reproductive-aged women (Moholdt and Hawley, 2020).

In mice fed a high-fat diet, time-restricted feeding combined with aerobic exercise training attenuated fat mass gain and adverse metabolic changes in lipid metabolism, insulin signaling, and glycemic control (Vieira et al., 2021). Previous human investigations have determined the effect of combined TRE and endurance exercise training on body composition and performance parameters in trained individuals (Brady et al., 2021; Moro et al., 2020; Tovar et al., 2021), but little is known about the metabolic benefits of this combined therapy in a sedentary population with overweight/obesity. Accordingly, the aim of this study was to investigate the isolated and combined effects of TRE and HIIT on glycemic control and cardiometabolic health outcomes in women with overweight/obesity. We hypothesized that isolated and combined TRE and HIIT would improve glycemic control after 7 weeks of intervention compared with a control group, and that a combination of TRE and HIIT would induce greater improvements compared with each strategy alone.

RESULTS

We conducted a 7-week randomized controlled trial with four parallel groups: TRE (energy intake limited to a $\leq$10-h eating window every day), HIIT (three supervised treadmill exercise sessions per week), a combination (TREHIIT), and a control group (CON, no intervention). The study protocol was published previously (Moholdt et al., 2021a). Figure 1 provides a schematic of the study design. Briefly, fasting blood samples; a 2-h 75 g oral glucose tolerance test (OGTT), during which blood was sampled every 30 min; blood pressure (BP) and resting heart rate (HR) measurements; analysis of body composition; and physical activity and sleep questionnaires were undertaken at baseline and after the interventions. On a separate day, both at baseline and upon completion of the interventions, the participants performed a cardiorespiratory fitness test to determine peak oxygen uptake (VO_2peak). One week of baseline measurements commenced directly after completed laboratory pre-assessments and randomization, followed by 7 weeks of intervention. Assessments after the intervention period were undertaken 48–72 h after the last exercise session for participants in HIIT and TREHIIT, whereas TRE was maintained until the evening before the assessments.

The primary outcome was change in total area under the glucose curve (tAUC) during the 2-h OGTT. Secondary outcomes were fasting plasma concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, leptin, adiponectin, and glycated hemoglobin (HbA1c); fasting, 30-min, and 120-min plasma insulin concentrations; 2-h incremental area under the glucose curve (iAUC); peak plasma glucose concentration during the OGTT; insulin resistance (HOMA2-IR); β cell responsiveness calculated as the change in insulin divided by the change in glucose over the first 30 min (insulinogenic index) (Seltzer et al., 1967); 2-h composite Matsuda insulin sensitivity index (Defronzo and Matsuda, 2010); insulin disposition index (Bergman et al., 2002); average 24-h and nocturnal (0000–0600 h) interstitial glucose levels; body composition; VO_2peak; systolic and diastolic BP; resting HR; subjective and objective physical activity levels; energy expenditure; objective sleep duration; subjective sleep quality; subjective appetite; energy intake; and macronutrient distribution.

Participants

We randomized 131 participants (TRE, n = 33; HIIT, n = 33; TREHIIT, n = 32; CON, n = 33) between August 12, 2019, and January 15, 2021. Figure 2 shows the flow of participants during the trial. Twenty-one participants dropped out of the study,

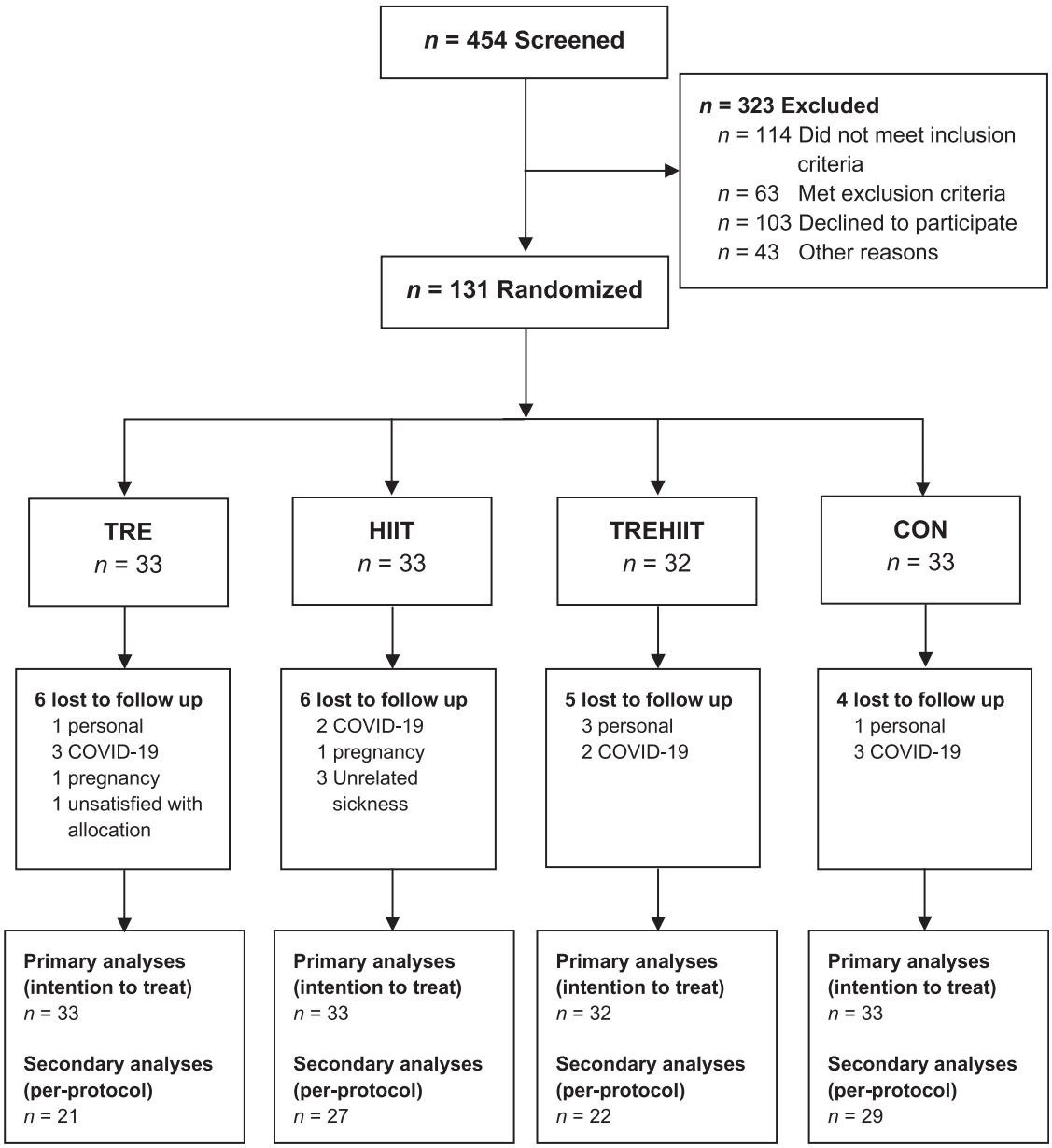

Figure 2. Trial profile

COVID-19: Participants lost to follow-up due to changes in physical activity and diet during the COVID-19 lockdown March–August 2020 or who were no longer interested in continuing the intervention after laboratory re-opening in August 2020. BMI, body mass index; CON, control; HIIT, high-intensity interval training; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training.

ten due to COVID-19. Of the participants allocated to CON, 18 chose to receive a delayed treatment after they completed the study. Table 1 shows baseline characteristics of all randomized participants.

Intention-to-treat analyses

All randomized participants were included in the intention-to-treat analyses, regardless of adherence to the interventions and/or completeness of outcome measures. The results are shown in Table 2.

Isolated and combined TRE and HIIT did not improve glycemic control during an OGTT

We collected data for the primary outcome (glucose tAUC) for 125 (95%) participants at baseline and for 106 (80%) post-intervention. There was no statistically significant effect of any of the interventions on glucose tAUC compared with CON (TRE, −26.3 mmol min/L; 95% CI, −82.3 to 29.7, p = 0.36; HIIT, −53.8 mmol min/L; 95% CI, −109.2 to 1.6, p = 0.057; TREHIIT, −41.3 mmol min/L; 95% CI, −96.4 to 13.8, p = 0.14) (Table 2; Figure 3).

Table 1. Baseline characteristics of all randomized participants according to group

	CON (n = 33)		TRE (n = 33)		HIIT (n = 33)		TREHIIT (n = 32)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age, years	33	36.4 (6.2)	33	36.2 (5.9)	33	34.9 (7.0)	32	37.3 (5.7)
Height, cm	33	169.6 (6.2)	33	169.3 (5.6)	33	167.5 (4.7)	32	168.0 (5.6)
Weight, kg	33	95.0 (11.2)	33	91.0 (10.8)	33	91.3 (13.0)	32	88.2 (10.3)
BMI, kg/m^2	33	33.1 (4.2)	33	31.8 (3.3)	33	32.5 (4.5)	32	31.4 (4.0)
Hormonal contraceptives, no. (%)	33	18 (55%)	33	19 (58%)	33	20 (61%)	32	16 (50%)
Fat mass, kg	33	39.5 (10.1)	33	37.3 (7.6)	33	38.6 (10.5)	32	35.8 (8.4)
Muscle mass, kg	33	31.0 (3.1)	33	30.0 (2.9)	33	29.3 (2.4)	32	29.2 (2.6)
Visceral fat area, cm^2	33	187.4 (48.5)	33	180.0 (34.8)	33	185.1 (47.7)	32	172.3 (38.3)
Systolic BP, mmHg	33	122.4 (10.3)	33	121 (10.7)	33	122.6 (10.1)	32	124.5 (10.9)
Diastolic BP, mmHg	33	80.4 (8.4)	33	79.9 (9.0)	33	78.8 (7.9)	32	82.6 (8.3)
Resting heart rate, bpm	33	71.0 (9.1)	33	70.3 (8.1)	33	71.9 (9.5)	32	69.9 (11.5)
Fasting glucose, mmol/L	32	5.0 (0.4)	33	5.0 (0.5)	33	4.9 (0.4)	32	4.9 (0.4)
Glucose tAUC, mmol·min/L	31	723.9 (133.1)	31	747.7 (162.0)	32	733.9 (128.2)	31	699.9 (118.7)
Glucose iAUC, mmol·min/L	31	135.3 (114.4)	31	150.0 (138.4)	32	141.8 (122.1)	31	112.3 (97.5)
Peak glucose, mmol/L	31	7.5 (1.3)	31	7.7 (1.8)	32	7.4 (1.4)	31	7.4 (2.0)
Fasting insulin, μIU/mL	28	20.4 (8.7)	26	17.7 (5.7)	27	17.7 (7.5)	25	18.0 (7.8)
30-min insulin, μIU/mL	28	74.6 (27.2)	24	85.8 (31.4)	27	88.6 (43.9)	25	77.4 (24.8)
120-min insulin, μIU/mL	28	42.8 (41.6)	25	48.6 (26.2)	26	51.1 (38.0)	24	42.2 (27.8)
HOMA2-IR	28	2.6 (1.1)	26	2.2 (0.7)	27	2.2 (0.9)	25	2.3 (0.9)
HbA1c, mmol/mol	31	33.8 (3.0)	32	34.5 (2.9)	33	33.1 (3.5)	30	34.6 (3.6)
Total cholesterol, mmol/L	31	4.8 (1.1)	32	4.7 (0.7)	33	4.8 (0.7)	30	4.7 (0.7)
HDL cholesterol, mmol/L	31	1.3 (0.3)	32	1.3 (0.3)	33	1.4 (0.3)	30	1.4 (0.3)
LDL cholesterol, mmol/L	31	3.0 (1.1)	32	3.2 (0.7)	33	3.3 (0.8)	30	3.3 (0.7)
Triglycerides, mmol/L	31	1.2 (0.6)	32	1.3 (0.5)	33	1.1 (0.4)	40	1.0 (0.4)
Adiponectin, μg/mL	26	9.3 (5.2)	25	11.1 (5.1)	26	9.6 (4.8)	24	10.5 (5.0)
Leptin, ng/mL	26	36.0 (21.9)	26	36.6 (14.5)	25	39.1 (21.2)	25	39.1 (16.3)
VO_2peak, L/min	33	3.2 (0.4)	33	3.1 (0.3)	33	3.1 (0.4)	32	3.0 (0.4)
VO_2peak, mL/min/kg	33	34.6 (5.7)	33	35.0 (5.0)	33	34.6 (6.1)	32	34.8 (5.5)
Maximal heart rate, bpm	33	186.7 (9.9)	33	189.2 (7.0)	33	188.1 (10.1)	32	188.8 (7.9)
Heart rate recovery, bpm	33	32.4 (7.2)	33	33.8 (10.4)	33	30.2 (9.8)	32	32.0 (8.6)

Data are for n participants in each group presented as descriptive mean with SD, if not otherwise noted. BP, blood pressure; BMI, body mass index; CON, control; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HIIT, high-intensity interval training; HOMA2-IR, homeostatic assessment of insulin resistance; iAUC, incremental area under the curve; LDL, low-density lipoprotein; tAUC, total area under the glucose curve; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training; VO_2peak, peak oxygen uptake.

TRE and TREHIIT induced improvements in secondary glycemic control outcomes

TREHIIT reduced long-term glycemic control (HbA1c) by 1.1 mmol/mol. Nocturnal glucose was reduced by 0.4 mmol/L after TRE. There were tendencies for improvements (p values between 0.01 and 0.05) in OGTT peak glucose after HIIT and TREHIIT, 30-min insulin concentration after TREHIIT, nocturnal glucose after TREHIIT, and 24-h glucose after TRE (Table 2; Figure 3). There were no statistically significant differences in other secondary glycemic control outcomes (Table 2).

Combined TRE and HIIT had an additive effect on fat mass loss

All intervention groups decreased body weight, fat mass, and visceral fat area compared with CON, with significantly greater reductions (2-fold) after TREHIIT compared with isolated TRE and HIIT. There were no significant changes in muscle mass after any intervention compared with CON (Figure 4).

HIIT and TREHIIT induced similar improvements in cardiorespiratory fitness, but had little effect on other cardiometabolic health markers

Both HIIT and TREHIIT improved VO_2peak by ~3 mL/kg/min (9%), while there were no improvements in cardiorespiratory fitness after isolated TRE (Table 2). There were no statistically significant differences in blood lipids, appetite hormones, or vital signs after any of the interventions compared with CON ($p > 0.01$), but tendencies of reduced leptin and HDL after TREHIIT (Table 2).

Adherence was high in all intervention groups

Participants in TRE and TREHIIT adhered to a ≤10-h eating window for 6.2 (SD 0.8) and 6.1 (SD 0.9) days/week, respectively. TRE and TREHIIT reduced their eating windows by 3.7 (95% CI,

Table 2. Intention-to-treat analyses of primary and secondary outcomes

	Measurement	Group	Baseline		After the intervention		Difference (group × time)			
							Compared with CON			Compared with TREHIIT
			n	Mean (SD)	n	Mean (SD)	Estimated effect	95% CI	p value	p value
Primary outcome										
	Glucose tAUC, mmol•min/L	CON	31	723.9 (133.1)	28	744.6 (132.8)				
		TRE	31	747.7 (162.0)	25	730.8 (136.0)	−26.3	−82.3 to 29.7	0.36	0.60
		HIIT	32	733.9 (128.2)	26	692.2 (120.5)	−53.8	−109.2 to 1.6	0.057	0.66
		TREHIIT	31	699.9 (118.7)	27	693.2 (137.8)	−41.3	−96.4 to 13.8	.14	
Secondary outcomes										
Glycemic control	HbA1c, mmol/mol	CON	31	33.8 (3.0)	27	34.2 (2.8)				
		TRE	32	34.5 (2.9)	26	34.7 (3.1)	−0.5	−1.3 to 0.3	0.19	0.17
		HIIT	33	33.1 (3.5)	26	32.9 (4.0)	−0.7	−1.5 to 0.1	0.096	0.30
		TREHIIT	30	34.6 (3.6)	26	33.9 (3.5)	−1.1	−1.9 to −0.3	0.008	
	Glucose iAUC, mmol•min/L	CON	31	135.3 (114.4)	28	144.2 (133.6)				
		TRE	31	150.0 (138.4)	25	147.6 (129.5)	−6.6	−59.5 to 46.2	0.80	0.57
		HIIT	32	141.8 (122.1)	26	119.9 (109.9)	−31.0	−83.3 to 21.3	0.24	0.74
		TREHIIT	31	112.3 (97.5)	27	115.3 (122.7)	−22.1	−74.5 to 30.2	0.40	
	Peak glucose, mmol/L	CON	31	7.5 (1.3)	28	7.6 (1.3)				
		TRE	31	7.7 (1.8)	25	7.6 (1.4)	−0.3	−0.9 to 0.3	0.34	0.20
		HIIT	32	7.4 (1.4)	26	7.0 (1.3)	−0.6	−1.2 to −0.0	0.047	0.79
		TREHIIT	31	7.4 (2.0)	27	7.1 (1.8)	−0.7	−1.3 to −0.1	0.024	
	Fasting glucose, mmol/L[a]	CON	32	5.0 (0.4)	28	5.0 (0.4)				
		TRE	33	5.0 (0.5)	28	4.9 (0.5)	−0.1	−0.3 to 0.2	0.60	0.39
		HIIT	33	4.9 (0.4)	26	4.8 (0.5)	−0.2	−0.5 to 0.1	0.18	0.95
		TREHIIT	32	4.9 (0.4)	27	4.8 (0.4)	−0.2	−0.4 to 0.0	0.085	
	Fasting insulin, μIU/mL	CON	28	20.4 (8.7)	27	18.9 (9.6)				
		TRE	26	17.7 (5.7)	25	17.3 (6.5)	0.6	−2.6 to 3.7	0.72	0.41
		HIIT	27	17.7 (7.5)	25	17.0 (9.2)	0.3	−2.8 to 3.5	0.83	0.50
		TREHIIT	25	18.0 (7.8)	26	15.9 (7.2)	−0.8	−3.9 to 2.3	0.63	
	30-min insulin, μIU/mL[a]	CON	28	74.6 (27.2)	27	86.4 (30.9)				
		TRE	24	85.8 (31.4)	23	82.9 (28.6)	−10.4	−23.8 to 1.0	0.20	0.38
		HIIT	27	88.6 (43.9)	25	83.8 (30.5)	−12.4	−28.6 to 0.5	0.20	0.62
		TREHIIT	25	77.4 (24.8)	26	71.1 (24.1)	−17.1	−29.2 to −6.4	0.012	
	120-min insulin, μIU/mL[a]	CON	28	42.8 (41.6)	27	42.4 (33.2)				
		TRE	25	48.6 (26.2)	23	51.4 (35.0)	4.9	−9.1 to 17.9	0.68	0.55
		HIIT	26	51.1 (38.0)	24	44.2 (23.4)	−0.7	−17.5 to 15.4	0.96	0.92
		TREHIIT	24	42.2 (27.8)	25	31.4 (28.4)	0.2	−14.3 to 16.1	0.99	

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Table 2. ***Continued***

	Measurement	Group	Baseline		After the intervention		Difference (group × time)			
							Compared with CON			Compared with TREHIIT
			n	Mean (SD)	n	Mean (SD)	Estimated effect	95% CI	p value	p value
	HOMA2-IR	CON	28	2.6 (1.1)	27	2.4 (1.2)				
		TRE	26	2.2 (0.7)	25	2.2 (0.8)	0.1	−0.3 to 0.4	0.79	0.42
		HIIT	27	2.2 (0.9)	25	2.1 (1.2)	0.0	−0.4 to 0.4	0.94	0.53
		TREHIIT	25	2.3 (0.9)	26	2.0 (0.9)	−0.1	−0.5 to 0.3	0.57	
	Insulinogenic index[a]	CON	28	1.2 (2.9)	27	0.1 (6.4)				
		TRE	23	0.71 (5.3)	23	1.9 (1.1)	1.8	−0.2 to 4.3	0.27	0.42
		HIIT	27	2.0 (1.7)	25	1.7 (3.2)	1.4	−0.4 to 2.4	0.36	0.24
		TREHIIT	25	1.9 (1.2)	26	4.2 (8.2)	3.9	1.1 to 5.6	0.18	
	2-h composite Matsuda insulin sensitivity index	CON	28	5.5 (3.5)	27	5.6 (3.3)				
		TRE	25	4.5 (1.9)	23	4.9 (2.5)	−0.1	−1.2 to 1.0	0.86	0.94
		HIIT	26	5.0 (2.8)	24	5.6 (3.7)	0.3	−0.8 to 1.4	0.63	0.57
		TREHIIT	24	5.4 (2.9)	25	5.7 (2.9)	−0.1	−1.1 to 1.0	0.92	
	Insulin disposition index[a]	CON	28	5.2 (15.9)	27	−0.0 (43.6)				
		TRE	23	3.7 (20.1)	23	8.9 (6.4)	9.4	−2.8 to 24.3	0.32	0.28
		HIIT	26	11.8 (17.3)	24	16.9 (30.3)	14.2	−4.4 to 29.9	0.25	0.45
		TREHIIT	24	10.4 (10.6)	25	25.7 (45.1)	23.8	1.0 to 43.1	0.19	
	Nocturnal glucose, mmol/L	CON	29	4.7 (0.4)	26	4.8 (0.5)				
		TRE	26	4.6 (0.5)	26	4.3 (0.5)	−0.4	−0.7 to −0.2	<0.001	0.15
		HIIT	27	4.6 (0.4)	26	4.5 (0.5)	−0.2	−0.4 to 0.1	0.14	0.42
		TREHIIT	27	4.5 (0.6)	26	4.4 (0.4)	−0.3	−0.5 to −0.0	0.024	
	24-h glucose, mmol/L	CON	29	5.1 (0.4)	26	5.1 (0.4)				
		TRE	26	5.1 (0.4)	26	4.9 (0.4)	−0.2	−0.4 to −0.0	0.016	0.09
		HIIT	27	5.0 (0.4)	26	4.9 (0.3)	−0.1	−0.3 to 0.1	0.19	0.56
		TREHIIT	27	4.9 (0.4)	25	5.0 (0.5)	−0.1	−0.3 to 0.1	0.48	
Body composition	Weight, kg	CON	33	95.0 (11.2)	29	94.2 (12.0)				
		TRE	33	91.0 (10.8)	29	89.4 (12.3)	−2.1	−3.2 to −1.0	<0.001	0.012
		HIIT	33	91.3 (13.0)	26	90.4 (13.8)	−1.7	−2.8 to −0.5	0.005	0.001
		TREHIIT	32	88.2 (10.3)	27	84.9 (10.6)	−3.6	−4.7 to −2.5	<0.001	
	Fat mass, kg	CON	33	39.5 (10.1)	29	38.4 (10.4)				
		TRE	33	37.3 (7.6)	29	35.9 (8.8)	−1.6	−2.5 to −0.6	<0.001	0.001
		HIIT	33	38.6 (10.5)	26	37.7 (11.7)	−1.5	−2.4 to −0.5	0.002	<0.001
		TREHIIT	32	35.8 (8.4)	27	33.2 (8.9)	−3.1	−4.1 to −2.2	<0.001	
	Muscle mass, kg	CON	33	31.0 (3.1)	29	31.1 (3.2)				
		TRE	33	30.0 (2.9)	29	29.7 (3.0)	−0.4	−0.7 to −0.0	0.039	0.65

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Table 2. ***Continued***

	Measurement	Group	Baseline		After the intervention		Difference (group × time)			
							Compared with CON			Compared with TREHIIT
			n	Mean (SD)	n	Mean (SD)	Estimated effect	95% CI	p value	p value
		HIIT	33	29.3 (2.4)	26	29.4 (2.3)	−0.1	−0.5 to 0.2	0.53	0.36
		TREHIIT	32	29.2 (2.6)	27	28.7 (2.6)	−0.3	−0.6 to 0.1	0.11	
	Visceral fat area, cm^2	CON	33	187.4 (48.5)	29	182.1 (50.1)				
		TRE	33	180.0 (34.8)	29	172.8 (42.4)	−8.0	−12.9 to −3.1	0.002	<0.001
		HIIT	33	185.1 (47.7)	26	177.1 (54.1)	−9.2	−14.3 to −4.2	<0.001	0.005
		TREHIIT	32	172.3 (38.3)	27	158.9 (42.8)	−16.8	−21.8 to −11.7	<0.001	
Cardiometabolic markers	VO_2peak, L/min	CON	33	3.2 (0.4)	29	3.2 (0.4)				
		TRE	33	3.1 (0.3)	27	3.1 (0.4)	−0.0	−0.1 to 0.1	0.82	0.018
		HIIT	33	3.1 (0.4)	26	3.3 (0.4)	0.2	0.1 to 0.3	<0.001	0.25
		TREHIIT	32	3.0 (0.4)	26	3.2 (0.4)	0.1	0.0 to 0.3	0.027	
	VO_2peak, mL/kg/min	CON	33	34.6 (5.7)	29	34.6 (6.0)				
		TRE	33	35.0 (5.0)	27	35.3 (5.3)	0.5	−0.8 to 1.9	0.44	<0.001
		HIIT	33	34.6 (6.1)	26	36.8 (5.9)	3.1	1.7 to 4.5	<0.001	0.64
		TREHIIT	32	34.8 (5.5)	26	38.1 (5.7)	3.4	2.0 to 4.8	<0.001	
	Systolic BP, mmHg	CON	33	122.4 (10.3)	29	122.6 (10.5)				
		TRE	33	121 (10.7)	28	118.7 (11.5)	−2.9	−6.4 to 0.6	0.11	0.023
		HIIT	33	122.6 (10.1)	26	121.5 (9.3)	−1.0	−4.6 to 2.6	0.58	0.21
		TREHIIT	32	124.5 (10.9)	26	124.7 (8.2)	1.3	−2.3 to 4.9	0.47	
	Diastolic BP, mmHg	CON	33	80.4 (8.4)	29	80.3 (9.9)				
		TRE	33	79.9 (9.0)	28	78.6 (10.1)	−1.6	−4.6 to 1.4	0.28	0.31
		HIIT	33	78.8 (7.9)	26	78.3 (8.0)	−0.8	−3.9 to 2.2	0.59	0.61
		TREHIIT	32	82.6 (8.3)	26	81.5 (5.7)	−0.0	−3.1 to 3.0	0.98	
	Resting heart rate, bpm	CON	33	71.0 (9.1)	29	71.2 (10.3)				
		TRE	33	70.3 (8.1)	28	71.2 (9.2)	0.5	−3.5 to 4.5	0.80	0.03
		HIIT	33	71.9 (9.5)	26	68.0 (9.5)	−3.4	−7.5 to 0.7	0.10	0.75
		TREHIIT	32	69.9 (11.5)	26	67.5 (11.8)	−4.1	−8.1 to 0.0	0.051	
	Total cholesterol, mmol/L	CON	31	4.8 (1.1)	27	4.6 (1.1)				
		TRE	32	4.7 (0.7)	26	4.7 (0.6)	0.1	−0.2 to 0.3	0.53	0.05
		HIIT	33	4.8 (0.7)	26	4.5 (0.6)	−0.2	−0.4 to 0.1	0.19	0.96
		TREHIIT	30	4.7 (0.7)	26	4.6 (0.7)	−0.2	−0.4 to 0.1	0.17	
	HDL cholesterol, mmol/L	CON	31	1.3 (0.3)	27	1.3 (0.3)				
		TRE	32	1.3 (0.3)	26	1.3 (0.2)	−0.02	−0.09 to 0.05	0.59	0.062
		HIIT	33	1.4 (0.3)	26	1.4 (0.3)	−0.04	−0.11 to 0.03	0.26	0.20
		TREHIIT	30	1.4 (0.3)	26	1.3 (0.3)	−0.08	−0.15 to −0.02	0.016	

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Table 2. ***Continued***

Measurement	Group	Baseline		After the intervention		Difference (group × time) Compared with CON			Compared with TREHIIT
		n	Mean (SD)	n	Mean (SD)	Estimated effect	95% CI	p value	p value
LDL cholesterol, mmol/L	CON	31	3.4 (1.1)	27	3.3 (1.1)				
	TRE	32	3.2 (0.7)	26	3.3 (0.7)	0.07	−0.17 to 0.30	0.56	0.043
	HIIT	33	3.3 (0.8)	26	3.1 (0.8)	−0.19	−0.42 to 0.05	0.12	0.94
	TREHIIT	30	3.3 (0.7)	26	3.2 (0.7)	−0.18	−0.41 to 0.06	0.14	
Triglycerides, mmol/L	CON	31	1.2 (0.6)	27	1.1 (0.5)				
	TRE	32	1.3 (0.5)	26	1.2 (0.5)	0.05	−0.14 to 0.23	0.63	0.92
	HIIT	33	1.1 (0.4)	26	1.1 (0.4)	0.04	−0.15 to 0.23	0.66	0.95
	TREHIIT	30	1.0 (0.4)	26	1.1 (0.5)	0.04	−0.16 to 0.23	0.71	
Adiponectin, μg/mL[a]	CON	26	9.3 (5.2)	26	9.4 (4.9)				
	TRE	25	11.1 (5.1)	24	10.1 (4.1)	−0.5	−1.7 to 0.6	0.45	0.99
	HIIT	26	9.6 (4.8)	25	8.3 (4.2)	−1.0	−2.3 to 0.2	0.13	0.66
	TREHIIT	24	10.5 (5.0)	24	9.9 (5.8)	−0.6	−2.1 to 0.9	0.53	
Leptin, ng/mL[a]	CON	26	36.0 (21.9)	25	35.1 (22.2)				
	TRE	26	36.6 (14.5)	25	32.7 (14.8)	−3.0	−13.1 to 6.8	0.60	0.027
	HIIT	25	39.1 (21.2)	24	30.5 (17.8)	−5.7	−15.5 to 3.1	0.34	0.12
	TREHIIT	25	39.1 (16.3)	25	25.1 (13.5)	−12.0	−21.1 to −3.2	0.021	

Observed data at baseline and after the intervention for n participants in each group, presented as descriptive mean with standard deviation (SD). The difference (group × time) is the mean change in the intervention group with estimate, corresponding 95% confidence intervals (95% CI), and p values compared with the control group (CON) and with p values compared with TREHIIT, by linear mixed-model analyses. BP, blood pressure; BMI, body mass index; CON, control; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HIIT, high-intensity interval training; HOMA2-IR, homeostatic assessment of insulin resistance; iAUC, incremental area under the curve; LDL, low-density lipoprotein; tAUC, total area under the glucose curve; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training; VO_2peak, peak oxygen uptake.

[a]95% CI and p values are from bootstrap with 3,000 samples and bias corrected and accelerated confidence intervals due to non-normally distributed residuals

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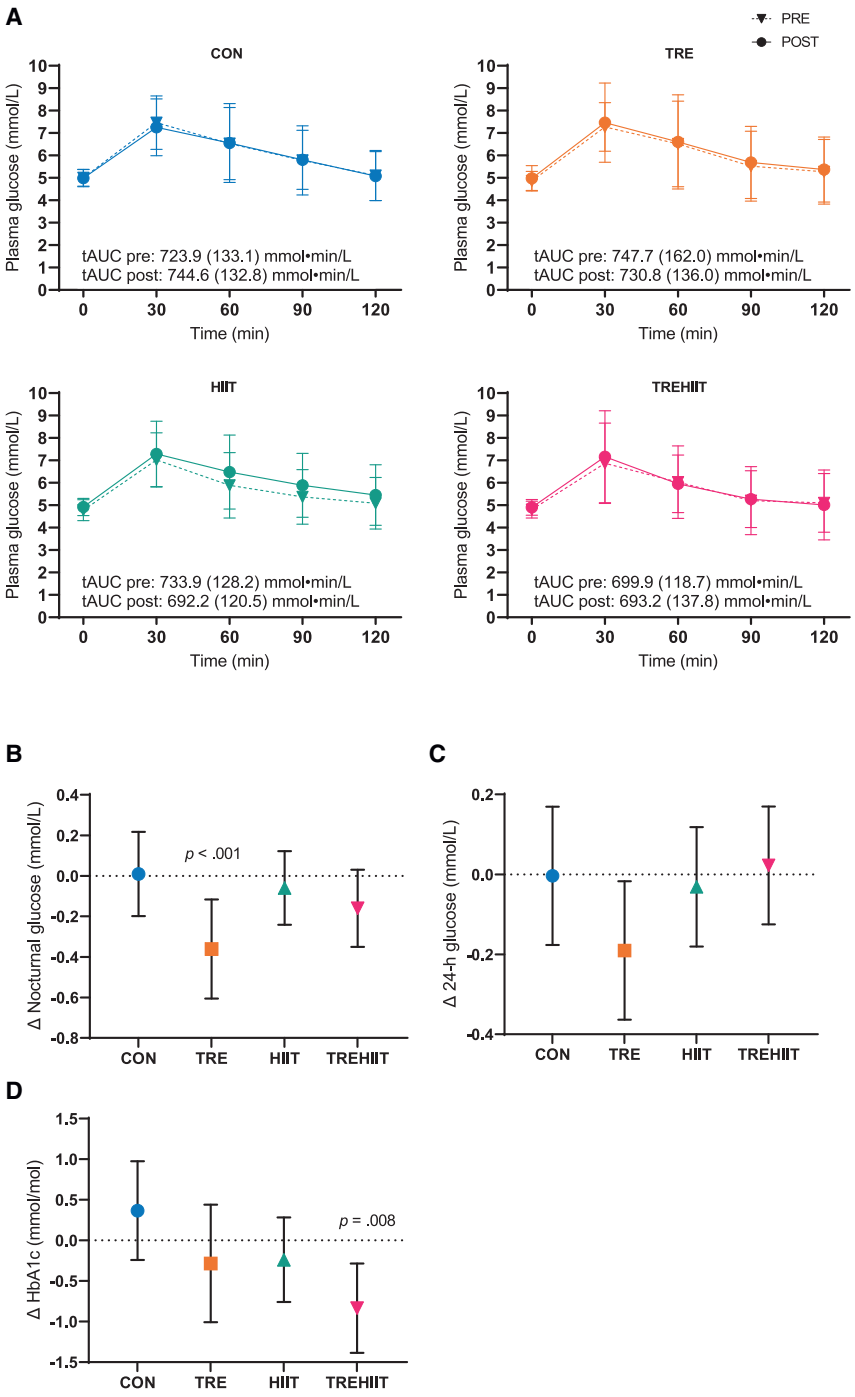

Figure 3. Isolated and combined TRE and HIIT did not improve glycemic control during an oral glucose tolerance test

TRE and combined TRE and HIIT improved secondary glycemic control outcomes.

(A) Pre- and post-intervention plasma glucose concentrations measured every 30 min during a 2-h 75 g oral glucose tolerance test, according to group. Descriptive statistics with means and SDs for the intention to treat population. Total area under the curve (tAUC) is observed means (SDs).

(B) Nocturnal interstitial glucose. Observed mean group changes from baseline to end of intervention. Descriptive statistics with means and SD for the intention to treat population.

(C) 24-h interstitial glucose. Observed mean group changes from baseline to end of intervention. Descriptive statistics with means and SD for the intention to treat population.

(D) HbA1c. Observed mean group changes from pre- to post-intervention. Descriptive statistics with means and SD for the intention to treat population. p values by linear mixed-model analyses, compared with the control group. CON, control; HIIT, high-intensity interval training; tAUC, total area under the glucose curve; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training.

−4.4 to −3.1, p < 0.001) and 3.0 h/day (95% CI, −3.6 to −2.4, p < 0.001), respectively, compared with baseline (Figure 5). At baseline, participants in TRE and TREHIIT consumed their first energy intake at 0835 h (SD 0.02 h) and 0852 h (SD 0.01 h), respectively, and their last energy intake at 2121 h (SD 0.01 h) and 2122 h (SD 0.01 h), respectively. During the intervention, participants in TRE consumed their first energy intake at 1020 h (SD 0.01 h) and their last energy intake at 1926 h (SD 0.02 h), while participants in TREHIIT consumed their first energy intake at 1001 h (SD 0.01 h) and their last energy intake at 1919 h (SD 0.01 h). The total daily energy intake was 8,652.5 (SD 2,029.2) in TRE, 8,359.6 (SD 1,623.4) in HIIT, 8,137.9 (SD 1,451.8) in TREHIIT, and 8,610.7 kJ/day (SD 1,815.9) in CON during the baseline week (Table S1). Participants in TRE and TREHIIT had a reduction in estimated daily energy intake of ∼840 kJ during the last 2 weeks of the intervention, compared with the baseline week, which would equate to an estimated weekly deficit of ∼5,900 kJ (Table S1). Participants in HIIT and CON did not change their total energy intake during the intervention period compared with baseline and consumed their first energy intake at ∼0900 h and last energy intake at ∼2120 h throughout the study (Figure 5; Table S1). None of the groups changed dietary macronutrient distribution from baseline to the end of intervention (Table S1). Figure 5 shows within-group differences and differences in the intervention groups compared with CON in subjective ratings of appetite at baseline, during the first week of intervention, and at the end of the intervention. Hunger and the desire to eat increased during the first week of intervention for participants in TRE and TREHIIT compared with those in CON but were no different from CON by the end of the intervention. Participants in HIIT and TREHIIT completed >90% of the scheduled exercise sessions and exercised at >90% maximal HR (HR_{max}) (Table S2). The energy expenditure induced by the three HIIT sessions was estimated to be ∼3,350 kJ/week, based on calculations from the

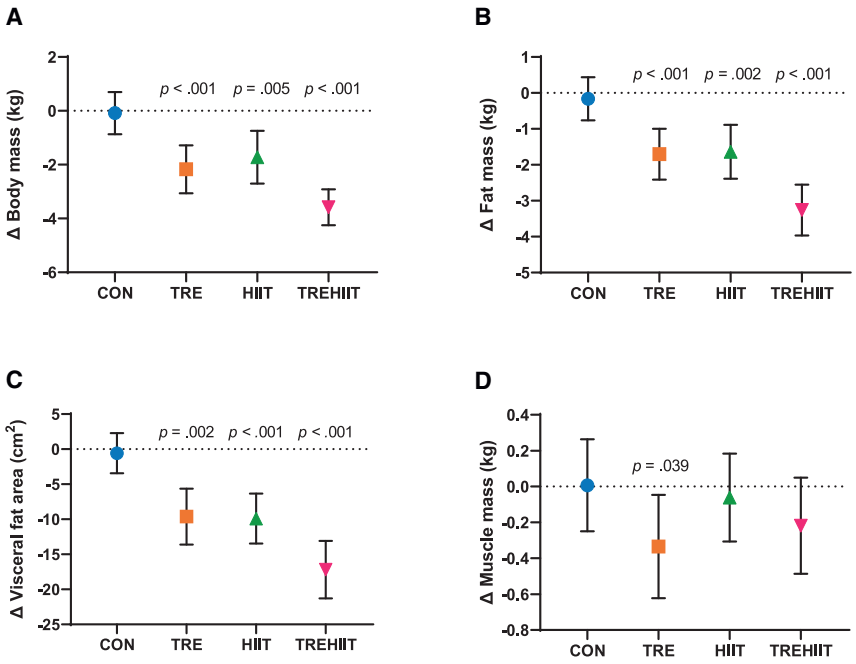

Figure 4. Combined TRE and HIIT had an additive effect on fat mass loss

Observed mean group changes in body composition from pre- to post-intervention. Descriptive statistics with means and SDs for the intention to treat population. (A) Body mass, (B) fat mass, (C) visceral fat area, and (D) muscle mass. p values by linear mixed-model analyses, compared with the control group. CON, control; HIIT, high-intensity interval training; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training.

participants' baseline VO_2peak, the rate of energy expenditure per liter of oxygen consumed (20.9 kJ/L), and the time spent exercising at 70% and 90% of HR_{max}. Physical activity levels, energy expenditure, sleep duration, and subjective sleep quality did not change in any group compared with CON (Table S3).

Per-protocol analyses

The secondary per-protocol analyses included only participants who adhered to their assigned protocol: participants in TRE with ≤10-h eating window on ≥5 days/week for 7 weeks, participants in HIIT with ≥16 HIIT sessions at ≥85% HR_{max}, and participants in TREHIIT who fulfilled both these criteria. Ninety-nine participants (TRE, n = 21; HIIT, n = 27; TREHIIT, n = 22; CON, n = 29) were included (Figure 2). Results from the per-protocol analyses were no different from the intention-to-treat analyses (Table S4).

Adverse events

There were no adverse events reported during the study, apart from the previously mentioned increases in feelings of hunger after TRE and TREHIIT during the first week of intervention.

DISCUSSION

In contrast to our principal hypothesis, 7 weeks of TRE, HIIT, or a combination failed to improve our primary outcome measure (glycemic control, determined by glucose tAUC during a 2-h OGTT) in reproductive-aged women with overweight/obesity. However, the combination of TRE and HIIT significantly reduced HbA1c compared with CON and induced greater losses in body weight, fat mass, and visceral fat area compared with either intervention alone. Isolated TRE resulted in lower nocturnal glucose concentrations compared with CON.

Improvements in many metabolic health biomarkers after TRE and HIIT interventions are more pronounced when undertaken by individuals with impaired fasting glucose (≥5.6 mmol/L) and HOMA-IR ≥ 3.18 at baseline (Kang et al., 2021; Jelleyman et al., 2015). For example, patients with type 2 diabetes mellitus had improved insulin sensitivity, fasting glucose, and HbA1c after 12 weeks of 10-h/day *ad libitum* TRE, compared with a usual-diet control group (Che et al., 2021). Women with polycystic ovary syndrome and HOMA-IR > 3.3 improved insulin sensitivity by 17% after 10 weeks of HIIT (Almenning et al., 2015). In the present study, most of the participants were normoglycemic at baseline, with limited prospect for a substantial change in our primary outcome variable. In individuals who are at risk of metabolic disease, but who are not yet clinically metabolically impaired, comprehensive lifestyle modifications may be necessary to induce substantial metabolic improvements. Indeed, HbA1c was only improved after the combined TREHIIT intervention. There were tendencies for a reduction in peak glucose and insulin concentrations after 30 min of the OGTT following TREHIIT. Reduced insulin levels early during an OGTT are indicative of improved β cell function, but we were unable to detect statistically significant improvements in either insulin sensitivity or β cell responsiveness indices after any intervention. In contrast, Sutton et al. (2018) reported increased β cell function after 5 weeks of early TRE (6-h eating window, with dinner before 1500 h) in men with overweight and prediabetes, despite no changes in either fasting glucose concentration or glucose levels during a 3-h OGTT (Sutton et al., 2018). Five weeks of early TRE has also been reported to improve insulin resistance in normal-weight individuals (Xie et al., 2022).

Human metabolism is primed for energy intake during the early waking hours, with insulin sensitivity and glucose tolerance greater upon waking than in the evening (Hawley et al., 2020). The reduced eating window and concomitant shift in the pattern of food intake to earlier in the day are likely to have underpinned the improved nocturnal glucose concentrations observed after the TRE intervention. Participants in TRE and TREHIIT delayed their habitual eating windows by almost 2 h in the morning and consumed their last meal of the day before ~2000 h during the intervention period. While a TRE window finishing earlier in the day may be advantageous for glycemic control compared with late TRE (Hawley et al., 2020; Hutchison et al., 2019; Xie et al., 2022), consuming an early dinner may be less compatible with family life and work schedules, potentially limiting the adherence to TRE (Parr et al., 2020a). The reduction in nocturnal glucose

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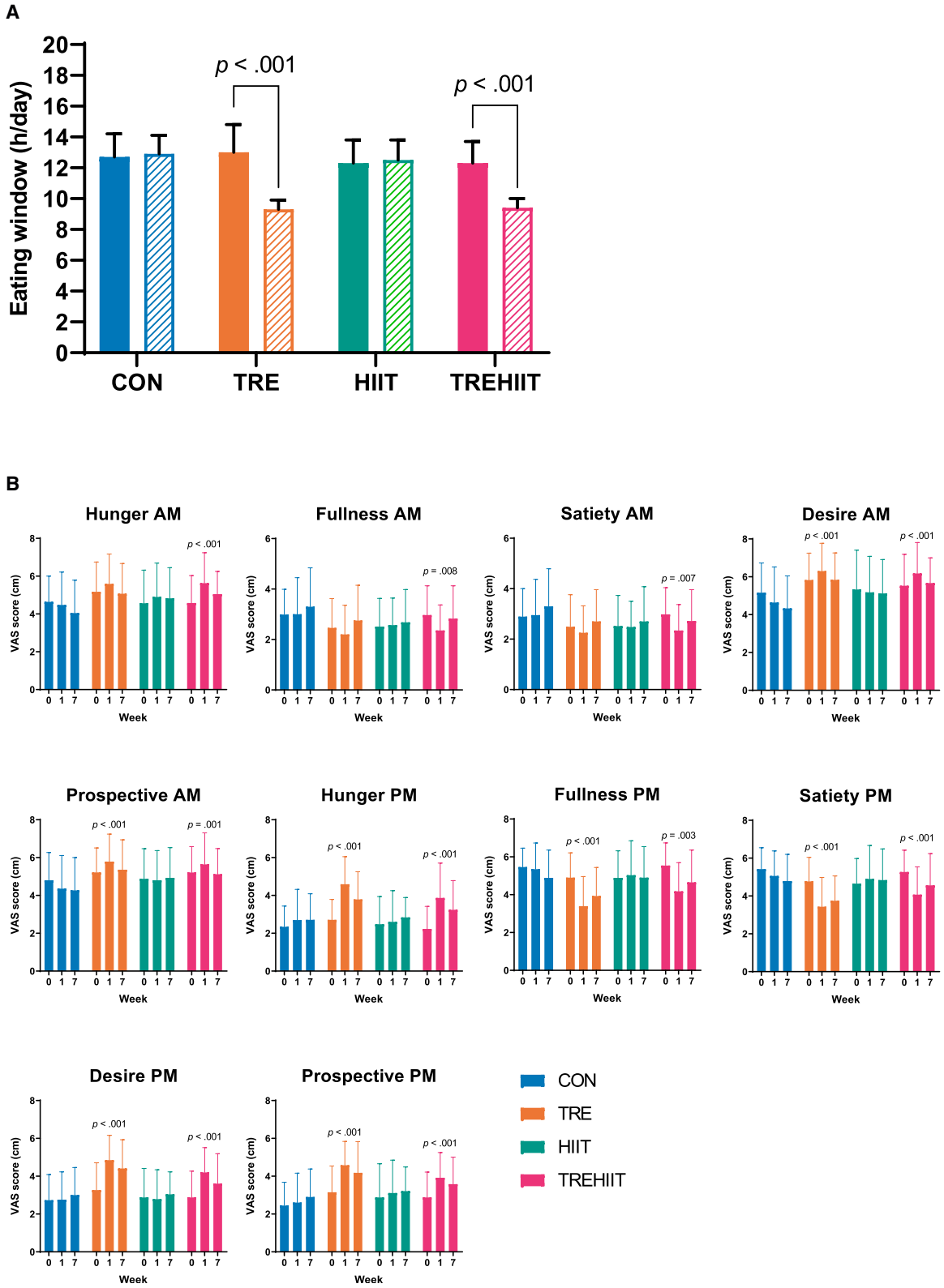

Figure 5. Eating window duration and subjective appetite

(A) Mean eating window duration at baseline and during the 7-week intervention period according to group. Descriptive statistics with means and SDs for the intention to treat population. Colored bars represent baseline eating window duration, while hatched bars represent interventional eating window duration. p values are for within-group differences by paired-sample t test.

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concentrations in our study in which participants self-selected their TRE window was of a similar magnitude (~0.2 mmol/L) as in studies of early TRE (0800–1400 h [Jamshed et al., 2019], 1000–1700 h [Parr et al., 2020a], and 0800–1700 h [Hutchison et al., 2019]), suggesting that even modest restrictions in the daily eating window can induce meaningful improvements in glycemic control. The previous studies (Hutchison et al., 2019; Parr et al., 2020a; Jamshed et al., 2019) employed crossover designs in mostly male subjects with overweight/obesity and were of shorter duration with small sample sizes, limiting direct comparisons with the current study.

We failed to detect significant improvements in glucose concentrations measured with continuous glucose monitors (CGMs) after the HIIT intervention. A recent meta-analysis reported that both acute and chronic exercise (aerobic, HIIT, and resistance training) reduced 24-h glucose by 0.5 mmol/L in individuals with type 2 diabetes mellitus (Munan et al., 2020). We have previously reported that aerobic exercise training, including HIIT, performed in the evening (1830 h), but not in the morning (0630 h), reduced nocturnal glucose concentrations compared with a non-exercise, high-fat diet control condition in men with overweight/obesity (Moholdt et al., 2021). The mechanisms underlying these observations are likely related to the impaired metabolic baseline status in individuals with type 2 diabetes mellitus (Munan et al., 2020) and an exercise-induced glucose uptake coinciding with the postprandial and circadian-related insulin-resistant state when performed in the evening (Moholdt et al., 2021; Savikj et al., 2019). In the current study, participants in HIIT were normoglycemic and performed all exercise sessions between 0700 and 1600 h. Furthermore, in metabolically healthy individuals, there is an increased hepatic glucose output in response to intense exercise and a period of hyperglycemia during and immediately after a training session (Marliss and Vranic, 2022), which could potentially mask any exercise-induced attenuation on daily glycemic control measured with CGMs in our HIIT and TREHIIT groups. Even in patients with type 2 diabetes mellitus, there is prolonged hyperglycemia after HIIT undertaken in the morning versus late afternoon (Savikj et al., 2019).

The combination of TRE and HIIT had an additive effect on the reductions in fat mass and visceral fat area, with an estimated treatment effect 2-fold greater than observed after each intervention in isolation. This finding agrees with results from a previous study on the isolated and combined effects of alternate-day fasting and endurance exercise (Bhutani et al., 2013). Even if TRE combined with HIIT is likely to induce a larger energy deficit compared with either strategy alone, the greater fat mass reduction observed in the TREHIIT group could also be due to a favorable metabolic switch toward a more oxidative phenotype, promoting lipid metabolism (Jaspers et al., 2017). In a rodent model, time-restricted feeding combined with endurance exercise increased fatty acid metabolism and prevented diet-induced fat mass gain (Vieira et al., 2021).

We observed no improvements in conventional blood lipid profiles after any of the interventions, although there was a tendency for reduced HDL cholesterol concentrations after TREHIIT. These findings contrast with the conclusions of a recent systematic review that reported beneficial effect of aerobic exercise training on all standard lipids in sedentary adults with three or more metabolic syndrome factors (Wood et al., 2019). The effect of TRE on blood lipid profiles is equivocal, although most studies report little or no change after short-term interventions (Kang et al., 2021). Studies of longer duration are needed to understand how the combination of TRE and HIIT affects blood lipid profiles.

Although TRE and HIIT can induce positive metabolic effects through mechanisms likely related to energy balance and nutrient handling (Jaspers et al., 2017; Parr et al., 2020b), exercise training alone produces only a modest increase in total daily energy expenditure with minimal effect on long-term weight loss (Parr et al., 2020b). In our study, the additional weekly energy expenditure induced by HIIT (~3,350 kJ/week) was less than the weekly energy deficit induced by TRE (~5,900 kJ). However, exercise training induces whole-body adaptations that are unlikely to be induced with diet alone, such as remodeling of the cardiovascular system and skeletal muscle tissue (Jaspers et al., 2017; Hawley et al., 2014). As such, exercise training imparts greater whole-body and tissue-specific metabolic health benefits than any current dietary intervention (Parr et al., 2020b). Some (Lowe et al., 2020; Cienfuegos et al., 2020; Chow et al., 2020; Liu et al., 2022) but not all (Gabel et al., 2018; Domaszewski et al., 2020) previous studies report a loss of lean mass after TRE interventions. In the current study, we observed an estimated reduction of 0.4 kg (95% CI, −0.7 to −0.0, p = 0.039) in muscle mass after TRE. Performing regular exercise is likely to be advantageous for reducing fat mass while preserving lean mass. While resistance training remains the gold standard for increasing muscle mass, the results from a recent study demonstrate that HIIT may provide sufficient stimulus to retain muscle mass during short-term weight loss (Callahan et al., 2021).

The structure and time-efficient features of TRE and HIIT are important for their potential compliance and adherence. The compliance to TRE in our study was ~6 days/week (86%), which is similar to that reported in populations of trained individuals and in adults with overweight/obesity (Kang et al., 2021), highlighting the feasibility of TRE as a sustainable dietary approach. Furthermore, TRE does not place strict constraints on types of foods consumed within the prescribed eating window. We did not observe any changes in food preference determined by the self-reported diet diaries, despite the reduced eating window. The specific features of TRE might address barriers to initiating dietary changes, such as having to avoid certain foods as required by low-energy and low-carbohydrate diets.

While TRE affected subjective feelings of hunger during the first week of the intervention, there were no differences in subjective ratings of appetite between the groups at the end of the intervention (Figure 5). We also observed high adherence and compliance to HIIT in our investigation, indicating that HIIT can be readily adopted by women with overweight/obesity.

(B) Observed mean scores of subjective appetite at baseline (week 0), the first week of intervention (week 1), and during the last week of intervention (week 7), according to group. Descriptive statistics with means and SD for the intention to treat population. p values by linear mixed-model analyses, compared with the control group. CON, control; HIIT, high-intensity interval training; TRE, time-restricted eating; TREHIIT, time-restricted eating and high-intensity interval training; VAS, visual analogue scale.

Such adherence rates were likely facilitated by the fully supervised exercise sessions, and it is uncertain whether such high rates would persist outside a structured study setting and over the long term (i.e., several months). Long-term adherence to lifestyle interventions remains an important issue in terms of their effectiveness in real-world settings. In the study by Liu et al. (2022), participants with overweight/obesity adhered to TRE (eating window between 0800 and 1600 h) on 84% of days during a 12- month intervention, supporting TRE as a sustainable dietary approach. Future follow-up studies and trials without close supervision are needed to investigate the feasibility of long-term TRE and HIIT. There were no reported adverse events related to TRE or HIIT in our study, indicating that TRE and HIIT can be safely implemented in similar populations.

In conclusion, our findings suggest that combining TRE with HIIT can rapidly induce several health benefits and decrease metabolic disease risk in women with overweight/obesity. The high rates of compliance and adherence highlight the potential of these diet-exercise protocols to be implemented in clinical practice for treatment and primary prevention of overweight/obesity. Given the multiple non-independent secondary outcome measures and risk of type I error, future studies are needed to confirm our findings and should investigate long-term effects and feasibility of these interventions by employing longer intervention durations.

Limitations of study

This study has several limitations. The intervention duration was only 7 weeks, which may have been too short to induce substantial changes in markers of glycemic control and other metabolic health outcomes, particularly for individuals with baseline glycemic outcomes within the normal physiological ranges. Furthermore, we cannot isolate the beneficial effects on metabolic health attributable to a reduced eating window and/or a potential reduction in energy intake in the TRE and TREHIIT groups, as energy restriction with TRE was not more effective for improving metabolic risk factors compared with energy restriction without TRE (Liu et al., 2022). Our power calculation was limited to detect differences between the HIIT and CON groups, and it is possible that we did not have sufficient statistical power to detect differences between the isolated interventions compared with TREHIIT. Another limitation is the use of bioelectrical impedance analysis to estimate body composition, which is less accurate than dual-energy X-ray absorptiometry in measuring body fat percentage and visceral fat (Bailey et al., 2018). Furthermore, hydration status was not standardized prior to the assessments in our study, which could affect our results, despite a relatively high inter-individual reliability of body composition measurements with the InBody 720 (Biospace) (Schubert et al., 2019). The COVID-19 outbreak could have influenced participants' habitual dietary and physical activity habits during this period, although any perturbations would be expected to be similar among groups. Last, this study included only reproductive-aged women, limiting the translation of our findings to males and other clinical populations.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2022.09.003.

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AUTHOR CONTRIBUTIONS

Conceptualization and methodology, T.M., J.A.H., and C.P.S.; investigation, K.L.H., C.P.S., S.S., M.G., and S.K.E.; data curation, K.L.H., S.S., and S.K.E.; formal analysis, S.L. and K.L.H.; writing – original draft, K.L.H.; writing – review & editing, K.L.H., J.A.H., T.M., and S.L.; supervision, T.M.; funding acquisition, T.M. and J.A.H. All authors approved the final draft for publication.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical commercial assays		
Human Leptin ELISA kit	IBL International GMBH	Cat#MD53001
Human Adiponectin ELISA kit	IBL International GMBH	Cat#30126762
Human Insulin ELISA kit	IBL International GMBH	Cat#RE53171
Deposited data		
Data S1 – Source data	This paper	N/A
Mendeley dataset	Elsevier Mendeley Data	Mendeley Data: https://doi.org/10.17632/4pgkkd54n3.1
Software and algorithms		
SPSS v.27	IBM	https://www.ibm.com/
GraphPad Prism v. 9.1.2	GraphPad Software	https://www.graphpad.com/
Microsoft PowerPoint v.2110	Microsoft	https://www.microsoft.com/
Sensewear Software v.8.1.0	BodyMedia	https://bodymedia-sensewear.software.informer.com/download/
Glyculator online software v.2.0	Medical University of Lodz, Department of Biostatistics and Translation Medicine	https://apps.konsta.com.pl/app/glyculator/
Other		
Pittsburgh Sleep Quality Index	Buysse et al. (1989)	https://www.cmu.edu/common-cold-project/measures-by-study/health-practices/sleep-habits/psqi_rev.pdf
International Physical Activity Questionnaire – Short-Form	Craig et al. (2003)	https://sites.google.com/site/theipaq/questionnaire_links
The Horne-Ostberg morningness-eveningness questionnaire	Horne and Ostberg (1976)	https://helse-bergen.no/seksjon/sovno/Documents/HornestbergMorningnessEveningnessQuestionnaireNorw.pdf
Polar H10 heart rate sensor	Polar, Finland	Cat#526371
Continuous Glucose Monitors Freestyle Libre Pro System	Abbott Diabetes Care Norway	Cat#71562; Cat#716871
Physical Activity Monitor Sensewear Pro	BodyMedia Sensewear Armband	N/A

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Trine Moholdt (trine.moholdt@ntnu.no).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The published article and supplemental information include datasets used to generate the graphs and figures in the paper (Data S1). Raw data from Tables 1, 2, S1, S3, and S4 and Figures 3, 4, and 5 have been deposited at Mendeley Data:https://doi.org/10.17632/4pgkkd54n3.1 and are publicly available as of the date of publication. All other data reported in this paper will be shared by the lead contact upon request. This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Human subjects

We recruited participants through public advertisements at the university homepages and in social media. Volunteers (n = 454) expressed their interest in participation via email to the principal investigator (Dr. Trine Moholdt) and were screened via phone call by the research investigators. Inclusion criteria were: female, aged 18–45 years, a body mass index (BMI) $\geq$ 27 kg/m^2, and able to walk on a treadmill or ride a bike for $\geq$60 min. Exclusion criteria were: pregnancy, breastfeeding $\leq$24 weeks prior to study commencement, cardiovascular disease, type 1 or 2 diabetes mellitus, taking anti-hypertension medication, glucose- or lipid-lowering medication, self-reported habitual eating window of $\leq$12 h/day, performing HIIT $\geq$1/week, variation in body mass $\geq$4 kg the last 3 months, or working nightshifts. A total of 131 participants were included and randomized 1:1:1:1 to one of the four study groups: TRE (n = 33), HIIT (n = 33), TREHIIT (n = 32), or CON (n = 33) (Figure 2). Participant characteristics can be found in Table 1. All participants provided written informed consent. The study protocol was approved by the Regional Committee for Medical and Health Research Ethics in North Norway (REK no. 2019/851).

Experimental design

The study was a single-center, four-armed, parallel group, randomized controlled trial undertaken at the Department of Circulation and Medical Imaging, Norwegian University of Science and Technology (NTNU), Trondheim, Norway, in accordance with the Helsinki Declaration. The study involved two separate days of baseline assessments prior to randomization, one baseline week, 7 weeks of intervention (or no intervention for participants allocated to CON) and two separate days of post-intervention assessments. Laboratory assessments were identical at baseline and after the 7-week intervention. One test day consisted of fasting blood samples, a 2-h 75-g oral glucose tolerance test (OGTT), measurement of vital signs and body composition analysis, and completion of three questionnaires; International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003), Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and Horne–Ostberg morningness eveningness Questionnaire (Horne and Ostberg, 1976). The other test day consisted of a cardiorespiratory fitness test. All assessments were scheduled to the follicular phase in women with regular menstrual cycles and participants were instructed to abstain from vigorous activity for $\geq$48 h prior to all measurements. One week of baseline measurements commenced directly after completed laboratory pre-assessments and randomization, during which participants were instructed to continue with their habitual dietary and physical activity pattern before initiating the assigned protocol on day eight. We requested all participants not to engage in other dietary or exercise regimens apart from the assigned protocols during the 7-week intervention period. We instructed the participants in TRE to limit all energy intake to a self-selected eating window of $\leq$10 h/day every day, with advice to consume the last meal no later than 2000 h, and without advice on macronutrient composition or total energy intake. Participants were free to consume non-energy-containing beverages (coffee, tea, and zero-calorie diet soda) during their fasting period. The exercise protocol consisted of three weekly, supervised treadmill HIIT sessions, although two participants who experienced physical limitations with treadmill walking/running trained on a stationary bike. Two of the weekly sessions consisted of 4 x 4-min work bouts at 90–95% maximal heart rate (HR_{max}), separated by 3 min moderate-intensity recovery, while the third session comprised 10 x 1-min work bouts at $\geq$ 90% of HR_{max} separated by 1 min low-intensity recovery. All sessions included a 10-min warm up at 60–70% HR_{max}, and a 3-min cool-down, for a total scheduled exercise time of 108 min/week. We recorded exercise intensity using HR monitors (Polar, Finland), treadmill speed and incline in all sessions. We adjusted speed and incline throughout the study to account for improvements in fitness during the intervention period to ensure compliance with the prescribed exercise intensity. Subjective ratings of perception of exertion (RPE) were taken after each completed work bout (Borg, 1982). We instructed the participants in TREHIIT to follow both TRE and HIIT, as described above. Participants in CON received no intervention but were asked to maintain their habitual physical activity and dietary habits throughout the study period. The investigators contacted all participants every week via phone/e-mail for motivational support. Assessments after the intervention period were undertaken 48–72 h after the last exercise session for participants in HIIT and TREHIIT, whereas TRE was maintained until the evening before the assessments for participants in TRE and TREHIIT. After completed post-assessments, participants allocated to CON were offered a delayed treatment in which they could choose one of the experimental interventions and received supervised exercise and/or weekly contact for 7 new weeks. We did not collect data from this delayed treatment period.

Protocol changes due to the COVID-19 outbreak

When laboratories closed on March 12, 2020, participants currently following the HIIT protocol continued with the remaining exercise sessions outdoors (supervised/unsupervised). Participants were provided with heart rate monitors (Polar, Finland), and data from outdoor sessions were uploaded to http://www.polarflow.com/ via the Polar Beat app on the participant's phone. Those who were randomized but had not yet started the intervention at the time were temporarily discontinued from the study (n = 6). When laboratories reopened in August 2020, the participants "on hold" were eligible for new baseline measurements and commencement of the previously assigned intervention if they reported no change to their diet or habitual physical activity or had a body mass variation of $\geq$4 kg within the lockdown period (n = 3). All protocol modifications were reported and approved by the Regional Committee of medical Research Ethics in North Norway.

METHOD DETAILS

Oral glucose tolerance test

The primary outcome was change in glycemic control measured as the total area under the plasma glucose curve (tAUC) during a 2-h OGTT. Participants attended the laboratory in the morning after a $\geq$10-h overnight fast. A study nurse placed an in-dwelling venous catheter in the participants' forearm. After a fasting blood sample was drawn, participants ingested 75 g of glucose diluted in 250 mL water (GlucosePro, Norges Naturmedisinsentral AS) within $\leq$5 min, after which blood was sampled every 30 min for 2 h. Serum and lithium heparin tubes rested in a vertical position for 30 min before being centrifuged at 2220 g and 20°C for 10 min. EDTA tubes were put on ice and centrifuged at 2220 g and 4°C for 10 min. Plasma glucose, HbA1c, and fasting concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were analyzed at St.Olav's Hospital's laboratories immediately after sampling, according to standard procedures. Aliquots of serum, plasma, and fullblood were stored at −80°C in a biobank for later analyses. Fasting, 30-min, and 120-min insulin, fasting adiponectin, and fasting leptin concentrations were measured in thawed plasma samples with enzyme-linked immunosorbent assay (ELISA, IBL-International, Hamburg, Germany) according to the manufacturer's instructions using a DS2 ELISA processing system (Dynex Technologies, Virginia, USA) at the research laboratories at the Department of Circulation and Medical Imaging, NTNU. We calculated glucose tAUC using the trapezoidal rule for glucose concentrations in blood sampled at 0, 30, 60, 90, and 120 min (Floch et al., 1990). We also determined 2-h incremental area under the glucose curve (iAUC) (Floch et al., 1990), peak plasma glucose concentration during the OGTT, and insulin resistance (HOMA2-IR) using the online HOMA2 calculator: https://www.dtu.ox.ac.uk/homacalculator/index.php (Wallace et al., 2004). The insulinogenic index was calculated as the change in plasma insulin concentration (μIU/mL) divided by the change in plasma glucose concentration (mg/dL) from 0 to 30 min during the OGTT (Seltzer et al., 1967). We estimated whole-body insulin sensitivity with the 2-h composite Matsuda insulin sensitivity index, using concentrations of plasma glucose (converted from mmol/L to mg/dL with conversion factor 18) and insulin (μIU/mL) at 0 and 120 min during the OGTT (Defronzo and Matsuda, 2010). The insulin disposition index was determined by the product of the 2-h composite Matsuda insulin sensitivity index and the insulinogenic index (Bergman et al., 2002). Missing data in the primary outcome measure and secondary blood biomarker outcomes were attributed to an inability to draw blood during the OGTT in some participants.

Body composition and vital signs

We used bioelectrical impedance analysis (InBody720, Biospace CO, Korea) to estimate the participants' total body mass, fat mass, muscle mass, and visceral fat area in the morning after a $\geq$10-h overnight fast, on the same day as the blood sampling. Height was measured using a standard stadiometer. Participants rested in a seated position for 15 min before we measured blood pressure (BP) and resting HR with an automatic blood pressure device (Philips IntelliVue MP50, Philips Medizin Systeme, Germany). BP and resting HR values were estimated from the average of three consecutive measurements taken 1 min apart.

Cardiorespiratory fitness test

The second test day consisted of an individualized, graded cardiorespiratory fitness test to estimate peak oxygen uptake (VO_2peak) using indirect calorimetry (MetaMax II Portable CPX System, Cortex, Germany). The participants walked or ran on a treadmill. After a 10-min warm-up at moderate intensity, we increased speed or inclination by 0.5–1.0 km/h or 1–2% every 1–2 min until participant volitional exhaustion, a plateau in O_2 uptake and/or a respiratory exchange ratio >1.10 was reached. We determined VO_2peak (in L/min and mL/min/kg) as the highest consecutive 30 s measured during the test. We recorded HR during the entire test using HR monitors (Polar, Finland) and used peak HR as an estimate of HR_{max}.

Diet, physical activity, and glucose monitoring

Participants were fitted with continuous glucose monitors (CGMs, FreeStyle Libre 2, Abbott Diabetes Care, Norway) and physical activity monitors (BodyMedia Sensewear Armband, Pittsburgh, PA) after randomization, which they wore for the first and last 14 days of the study. We instructed the participants to scan the glucose sensor inserted on the upper arm with the CGM device regularly $\geq$4 times/day. The screen of the CGM device was covered with duct tape to prevent participants from being aware of their glucose levels. We calculated average 24-h and nocturnal (0000–0600 h) interstitial glucose levels with the Glyculator 2.0 online software GlyCulator 2.0:konsta.com.pl. Some participants did not obtain sufficient data from the CGMs to estimate average nocturnal and/or 24-h interstitial glucose levels and were therefore excluded from these analyses. Raw CGM data were processed manually in Microsoft Excel. Glucose recordings the first 12 h after sensor insertion may be unreliable due to sensor acclimatization and were removed from the dataset. Days with missing glucose data accumulating to $\geq$4 h during daytime (0600 h–0000 h) and/or $\geq$2 h during nighttime (0000 h–0600 h) were removed from the dataset. Missing glucose data could be explained by user error (infrequent scans) or by the glucose sensor detaching prematurely. In the latter case, a new sensor was fitted within the same or the next day to complete the remaining days of recordings. Datasets left with a minimum of 4 days and 4 nights of complete recordings were included in the analyses. Baseline glucose levels were estimated from recordings during week 0, while glucose levels during the intervention were estimated from recordings during week 6 and 7. The physical activity monitor was kept on the opposite arm of the CGM sensor for the entire 14-day period and was only to be removed during showers/baths/saunas. From the physical activity monitor data, we determined average weekly physical activity in metabolic equivalent of task (METs)/day, average weekly energy expenditure (kJ/day), and average sleep duration (h/day), using the BodyMedia Sensewear 8.1 software program. Only participants with a daily

wear time of ≥95% on ≥4 days/week were included in the analyses. Baseline data were obtained from recordings during week 0, while interventional data were obtained from recordings during week 6 and 7. During the same 14-day periods, participants registered what they ate each day in an electronic food diary:https://www.kostholdsplanleggeren.no/ and rated subjective appetite on a visual analogue scale upon waking and before bedtime in a study-handbook. The time point of the first and last energy intake each day was self-reported in the study-handbook throughout the study.

Adherence

We calculated adherence to TRE as the average duration of the self-reported daily window for energy intake and the number of days per week with ≤10-h eating window. For HIIT, we calculated adherence as the percentage of the 21 scheduled exercise sessions completed, and compliance as the average percentage of HR_{max} from the last 2 min and the last 30 s of every work bout in the 4 x 4 and 10 x 1-min interval sessions, respectively.

QUANTIFICATION AND STATISTICAL ANALYSIS

Power and sample size

As there were no prior publications on the effect of TRE and/or the combination of TRE and HIIT for our primary outcome, we based the sample size calculation on a previous study of HIIT for 6 weeks in reproductive-aged women with overweight (Kuehnbaum et al., 2014). We required 24 participants in each group to detect a change of −54 (SD 64 mmol/L) in tAUC between HIIT and CON, with a statistical power of 80% and a significance level $\alpha = .05$ (based on a two-sided, independent t-test). With a predicted drop-out rate of 15%, difficulties obtaining all required blood samples for the primary outcome measure, and additional drop-outs due to the COVID-19 pandemic, we intended to include minimum 120 participants (30 in each group).

Randomization

Participants were randomized 1:1:1:1 to TRE, HIIT, a combination (TREHIIT), or CON, using a random number generator (The Unit for Applied Clinical Research, NTNU, Trondheim). The principal investigator (Dr. Trine Moholdt) performed the randomization of each participant after completed laboratory pre-assessments. Neither the participants nor the study investigators were blinded for group allocation.

Statistical analyses

The primary analyses included all obtained data irrespective of participant adherence to the interventions and completeness of outcome measures (intention to treat). We used linear mixed models with time, group, and their interactions as fixed effects, and subject as random effect (Twisk et al., 2018). The difference (time x group) is the mean change in the intervention group compared with CON, for which we report the estimate, corresponding 95% confidence intervals (CI) and p values. We checked normality of residuals by visual inspection of QQ-plots and performed bootstrapping with 3000 samples and bias corrected and accelerated CIs in cases of non-normal model residuals. In the intention to treat analyses, we adjusted for the baseline value by excluding any systematic main effect of group at baseline (Twisk et al., 2018). We used TREHIIT as reference group in secondary linear mixed model analyses to investigate differences in effect size between the interventional groups. Prespecified secondary per-protocol analyses included participants who adhered to their assigned protocol: participants in TRE with ≤10-h eating window on ≥ 5 days/week for 7 weeks, participants in HIIT with ≥16 HIIT sessions at ≥ 85% HR_{max}, and participants in TREHIIT who fulfilled both these criteria. In the per-protocol analyses, we used linear mixed models without baseline-adjustments by including the main effects of time, group, and their interactions, and subject as random effect. We analyzed within-group changes in the eating window using paired samples t-tests. We considered two-sided p values < .01 as statistically significant in all analyses, to protect against false positive findings due to multiple hypotheses. Statistical analyses were performed in IBM SPSS Statistics 27. Figures were generated in Microsoft PowerPoint for Microsoft 365 V. 2110 and GraphPad Prism 9.1.2.

ADDITIONAL RESOURCES

The trial was registered on: https://clinicaltrials.gov/ (NCT04019860), and the protocol article was published previously: https://bmjopen.bmj.com/content/11/2/e040020.