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Combined effects of time-restricted eating and exercise on short-term blood glucose management in individuals with Type 2 Diabetes Mellitus: The TREx study, a randomised controlled trial

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ABSTRACT

Aims: Time-restricted eating (TRE) is a chrono-nutrition strategy where the daily 'eating window' is reduced to 8–10 h. We investigated the acute (14-h) effects of TRE, with and without post-meal exercise, on blood glucose and insulin concentrations in people with type 2 diabetes mellitus.

Methods: Fourteen participants (5 F, 9 M; HbA1c: 7.6 ± 1.0%) completed four conditions in this randomised crossover study: CON (eating window, 0800–2000 h), CON with exercise (CON + Ex; 0800–2000 h + 15 min walking at 60% VO_2peak, 45 min post-meal), TRE (eating window 1000–1800 h), and TRE with exercise (TRE + Ex, 1000–1800 h + 15 min walking as per CON + Ex), with standardised meals. Venous blood samples were collected at 26-timepoints and analysed for glucose and insulin concentrations. Statistical analysis used linear mixed-effects models with $P < 0.05$.

Results: Reducing the eating window had little effect on plasma glucose 14-h area under the curve (AUC). Exercise reduced insulin 14-h AUC (P=0.01) with no additive effect of TRE.

Conclusion: Post-meal exercise lowered 14-h insulin AUC, neither 8-h TRE nor post-meal exercise altered 14-h blood glucose compared with 12-h eating window. Future work should focus on long-term effects of TRE combined with exercise for enhancing blood glucose in people with type 2 diabetes mellitus.

1. Introduction

Primary lifestyle interventions such as diet and exercise can improve glycaemic management in people with type 2 diabetes mellitus [1]. However, implementing and encouraging sustainable behaviour change strategies is challenging, and adherence is low [2–4]. Blood glucose excursions after eating induce transient postprandial hyperglycaemia, contributing to 30–40% of daily hyperglycaemia in people with type 2 diabetes mellitus [5]. Therefore, interventions that reduce postprandial excursions and encourage adherence are needed.

Time-restricted eating (TRE) aims to reduce the daily 'eating window' (i.e., eating between 8–10 h versus >12 h) to prolong the overnight fasting period [6,7]. TRE aligns the timing of the meals with biological circadian rhythms, optimising metabolic adaptations that enhance glucose management [8,9]. In people with type 2 diabetes mellitus, a delayed breakfast may also be beneficial to avoid eating at the same time

Abbreviations: ACU, Australian Catholic University; AUC, Area under the curve; CHO, Carbohydrate; CGM, Continuous glucose monitor; CPET, Maximal cardiopulmonary exercise testing; DXA, Dual-energy X-ray absorptiometry; ESM, Electronic supplementary material; HR, Heart rate; RMR, Resting metabolic rate; TRE, Time-restricted eating; TAG, Triglycerides.

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as the morning 'spike' in fasting glucose, the so-called 'dawn phenomenon' [10], as well as allowing for incidental activity to be accumulated before breakfast [11]. Consuming an earlier dinner may improve blood glucose due to increased insulin sensitivity [12].

TRE, when adhered to for at least five days of the week, improves glycaemic control in people with type 2 diabetes mellitus [13] and upregulates the expression of genes related to glucose uptake, the circadian clock, longevity, and autophagy in people with overweight and obesity [14]. TRE interventions of one to three months result in weight loss, fat loss and improved BP in people with metabolic syndrome and prediabetes [12,15], and lower HbA1c and improved insulin sensitivity in people with type 2 diabetes mellitus [16]. Furthermore, four to six months of 8-h TRE has beneficial effects on weight loss and HbA_{1c} [17,18], while prolonged (12 months) TRE reduces inflammatory markers and risk factors related to cardiovascular and metabolic diseases [19]. However, there is a lack of studies investigating the acute, one-day effects of TRE in the context of other behaviours, such as exercise, that might influence circadian rhythm or be used in conjunction with TRE.

Exercise is a potent stimulus known to influence both patterns of circadian rhythmicity and glucose management [20]. In people with type 2 diabetes mellitus, interrupting prolonged (7-h) sitting with activity bouts such as 3-min of light-intensity walking or resistance exercises every 30-min improves blood glucose excursions [21], and a 10-min walk after each main meal during the 1-h post-meal period improves blood glucose management compared with a single continuous 30-min walk bout at any time of the day [22]. In addition, a 15-min post-main meal walk attenuates postprandial hyperglycaemia [23], an independent risk factor for complications associated with type 2 diabetes mellitus [24]. It is currently unknown whether strategically-timed exercise combined with TRE results in an improvement in daily glucose management compared with TRE alone. The aim of the present study was to investigate the acute (14-h) effects of reducing the eating window from 12-h to 8-h, with and without post-prandial exercise after each main meal, on blood glucose and insulin concentrations in individuals with type 2 diabetes mellitus.

2. Methods

The present randomised crossover trial was conducted at the Australian Catholic University (ACU), Melbourne campus. The study commenced at the end of 2019 before being paused due to the COVID-19 pandemic. The study recommenced in May 2023 and completed in October 2023. Ethics approval was obtained from the ACU Human Research Ethics Committee (2019-61HC) and prospectively registered on the Australia New Zealand Clinical Trial Registry (ACTRN12619001222134). The study was conducted according to the Declaration of Helsinki, and participants provided written informed consent.

2.1. Participants and pre-trial measurements

Participants were recruited through emails via ACU database, TrialFacts recruitment company and the National Diabetes Services Scheme via an online screening questionnaire and follow-up phone call. Participants were recruited if they met the following inclusion criteria: aged 35 to 65 y with diagnosed type 2 diabetes mellitus, HbA1c between 6.5–9.9% (48–85 mmol/mol), BMI between 25–45 kg/m^2 and either diet-controlled or taking a maximum of two oral antihyperglycemic agents excluding sulphonylureas, insulin, and GLP-1 agonists. Exclusion criteria are shown in **Table S1**. Randomisation was via REDCap in blocks of four generated by an external colleague. Neither the research team nor the participants were blinded to the condition being performed. As the study was a cross-over design, the participants completed each of the four conditions, and were randomised to the order each condition was completed. Participants visited the laboratory on 12 occasions. At *Visit 1*, a glucose and anthropometric screening was performed, where a finger prick blood sample was obtained to determine HbA_{1c} (Cobas b 101 System, Roche, Switzerland). Height was measured using a wall stadiometer, and weight was recorded using digital scales. Hip and waist circumferences were measured with a metal tape measure. All measures were taken in duplicate, with a third measure taken if there was a difference of > 0.5 cm. If HbA1c and BMI inclusion criteria were met (HbA1c $<6.5\%$ and BMI between 25–45 kg/m^2) and a continued interest in participating in the study was confirmed, consent was obtained, and subsequent study visits were scheduled. Participants completed the Exercise and Sports Science Australia (ESSA) pre-screening tool to assess the ability to perform the exercise and a Morningness-Eveningness questionnaire (MEQ-SA) to assess the tendency to be a morning or evening person. A subsequent fasting visit *(Visit 2)* included a dual-energy X-ray absorptiometry (DXA) scan to assess body composition (GE Lunar iDXA Pro, encore software Version 16, USA) and an assessment of resting metabolic rate (RMR; ParvoMedics, TrueOneRMR, USA) to personalise energy consumption.

Maximal cardiopulmonary exercise testing (CPET) was conducted to measure peak oxygen uptake (VO_2peak; ParvoMedics, TrueOne 2400, USA) and individualise exercise intensity *(Visit 3)*. Participants started walking on a treadmill at 2.8–3.2 km/h, and the speed was increased by 0.5–1.0 km/h every 90 s. After reaching their maximal comfortable walking speed (indicated via hand signals), the incline was increased 0.5–1% every 90 s until participants reached volitional exhaustion. The peak 30 s average of VO_2 was taken as the VO_2peak. Electrocardiography (ECG) and blood pressure measurements were performed throughout the test. Participants were then fitted with a FreeStyle Libre Pro iQ (Abbott, USA) continuous glucose monitor (CGM), an accelerometer to measure physical activity (ActivPAL4^{TM}, Pal Technologies, Scotland), and a wrist-worn sleep monitor (ActiWatch Spectrum Plus, Phillips, Australia). Glucose and activity monitors were replaced every 14 days or when CGMs failed or dislodged.

2.2. Trial days

Participants completed four conditions in a randomised order: CON (eating window: 0800–2000 h), CON with exercise (CON + Ex; 0800–2000 h + 15 min walking at 60% peak aerobic capacity, 45 min post-meal), TRE (eating window 1000–1800 h), and TRE with exercise (TRE + Ex, 1000–1800 h + 15 min walking as per CON + Ex) with a three to seven-day washout between conditions (**Fig. 1**). Participants arrived at the laboratory at 0700 h for the day, left after the 2200 h blood sample and returned the next day at 0800 h. During trial days, participants remained seated except for structured exercise and at least four scheduled toilet breaks. Participants were encouraged to maintain their usual diet and physical activity throughout the study, they were asked to refrain from moderate/vigorous physical activity for 48-h and avoid consuming caffeine and alcohol for 24-h before each trial. Self-reported dietary intake was recorded using the Research Food Diary app (Xyris, Brisbane, Australia) or handwritten records 48-h before each trial. We had a maximum of two participants at a time, and therefore participants were in contact with each other.

A standardised dinner was provided for the night before each trial, and all meals were provided during each condition at standardised times (CON: at 0800 h, 1400 h and 2000 h; TRE: at 1000 h, 1400 h, and 1800 h; **Table S3**). The total daily energy distribution was ~25% breakfast, ~35% lunch and ~40% dinner. All meals had the same macronutrient composition intake (~45% carbohydrate, ~30% fat and ~25% protein), following the current Australian Healthy Eating Guidelines [25]. Individual energy intake was calculated from RMR with a physical activity factor of 1.4 and crosschecked with the Cunningham equation [26]. Standardised snacks (~290 kJ) were provided after each meal during exercise trials to match the energy cost of exercise, and water was consumed *ad libitum* in the first trial and was repeated in the subsequent trials. After each condition, participants were reimbursed with a gift

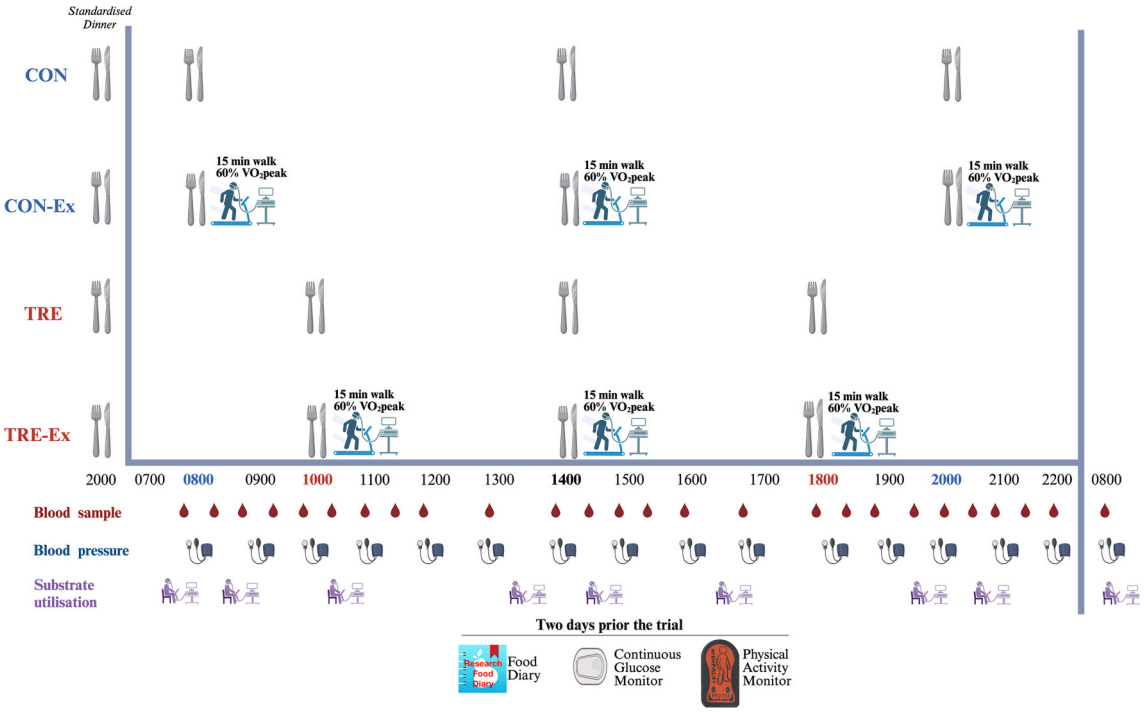

Fig. 1. Overview of the study design. Participants completed four conditions: CON (eating window: 0800–2000 h), CON with exercise (CON + Ex; 0800–2000 h + 15 min walking at 60% peak aerobic capacity, 45 min post-meal), TRE (eating window 1000–1800 h), and TRE with exercise (TRE + Ex, 1000–1800 h + 15 min walking as per CON + Ex), in a randomised order. Figure created in https://BioRender.com.

card.

2.3. Exercise and substrate utilisation

During the TRE + Ex and CON + Ex conditions, participants walked on a treadmill for 15 min at an intensity corresponding to ~60% VO_2peak, 45–60 min after each meal. During the exercise, heart rate (Polar Heart Rate Monitor, Polar Electro, Kempele, Finland), rate of perceived exertion [27], and substrate oxidation were measured. Substrate oxidation was measured using a face mask connected to a gas analyser for 25 min at 0735 h and the following morning at 0800 h and for 10 min at seven timepoints during each trial (0830 h, 1045 h, 1340 h, 1435 h, 1750 h, 1950 h, 2035 h).

2.4. Blood pressure and heart rate

Resting BP and heart rate (HR) were measured using the automated oscillatory method (ProBP 3400, Welch Allyn Inc, NY, USA). Participants remained in a seated upright position following a period of quiet rest, and measurements were obtained using an appropriately sized cuff with the participant's arm supported, according to current guidelines [28]. Two measurements, >1 min apart, of BP and HR were taken every hour (i.e., 15 measurements per trial day and one more measurement the morning after). A third measurement was taken if there was a difference of >5 mmHg between the first two measurements. Hourly BP and HR were reported as the average of the two measures.

2.5. Blood sampling

Whole blood samples (6 mL) were collected from an antecubital vein via an indwelling cannula into EDTA tubes hourly throughout the trial days and every 30 min in the 2-h post each meal. Immediately following each blood draw, 5 mL of saline was infused to keep the sample line patent and return a similar volume as the blood sample. The cannula was removed at the end of the trial day (i.e., after the 2200 h sample). A final blood sample was taken at 0800 h the following day via venepuncture. After collection, blood samples were centrifuged (centrifugation at 701.8 × g for 10 min at 4 °C), and plasma was stored at −80 °C for later analysis. Thawed plasma samples were analysed to measure the concentrations of insulin (Access 2 chemiluminescent immunoassay system, Beckman Coulter, California, USA), glucose, HbA1c, triglycerides, and non-esterified fatty acids (AU480, Beckman Coulter, California, USA). Additionally, gene expression was assessed from whole blood collected in 9 mL Tempus tubes at 0800, 1400, and 1600 h on day one and 0800 h on day two.

2.6. RNA isolation and Nanostring nCounter gene expression assay

Short-term TRE impacts the expression of genes related to glucose uptake, the circadian clock, longevity, and autophagy in people with overweight and obesity [29]. Therefore, we assessed the effect of acute TRE on gene expression in whole blood. Samples were collected in Tempus™ Blood RNA tubes at 0800, 1400, and 1600 h on day one and 0800 h on day two. Total RNA was extracted using the Tempus™ Blood RNA Isolation Kit (Applied Biosystems; Foster City, CA, USA) according to the manufacturer's instructions. RNA was quantified using a Qubit 4 Fluorometer (Thermo Fisher Scientific; Waltham, MA, USA). The Nanostring nCounter gene expression assay (Nanostring Technologies, Seattle, WA, USA) was used to quantify gene expression as previously described [30]. The full list of target genes and their accession numbers are given in **Table S4**. Briefly, customised probes carrying a unique fluorescent bar code were hybridized to RNA at 67 °C for >16 h. Probe sequences are given in **Table S5**. Purification and binding to the imaging membrane was performed using the nCounter prep station, after which the expression level of each target gene of interest was measured by counting the number of times the relevant barcode was detected using the nCounter Digital Analyzer. Gene counts were imported into the NanoString software nSolver, normalised using the geometric mean of six housekeeping genes (POLR2A, CDK4, ACTB, GAPDH, LDHA, and TBP), and analysed as fold change from baseline (0800 h on day 1).

2.7. Data analysis

All data (before and after the COVID-19 pandemic) was analysed collectively. The trapezoidal rule (baseline=0) was used to estimate the area under the curve (AUC) for the total glucose and insulin response over time using GraphPad Prism (Version 10.1.2, GraphPad Software, San Diego, USA). The total incremental AUC (iAUC) and postprandial 2-h iAUC were calculated using the first sample concentration. The 15 min post-meal walk was analysed using PALbatch software (V8.11.1.64 PAL-technologies Ltd., Glasgow, Scotland), and the step count was analysed utilising 1-min epochs. Physical activity for the 2-h after each meal was isolated to match the 2-h postprandial period. Means and standard deviations for substrate utilisation were calculated using Microsoft Excel. Standard equations were used to calculate rates of carbohydrate (CHO) and fat oxidation [31].

2.8. Statistical analyses

Power calculations were based on existing data [21], estimating that the effect size (Cohen's d) of acute one-day exposure to CON + Ex, relative to CON, was 1.8 (very large) for the primary outcome of glucose total AUC. Sample size calculation indicated that n=5 participants were required to detect an effect size of 1.8 with a power of 0.80 and α of 0.05. Due to the multiple comparisons and to account for an expected 20% attrition rate, we aimed to enrol 16 participants. Statistical analyses were performed using linear mixed models using R (version 4.3.2). The normality of the data was assessed using the Shapiro-Wilk Test. The '*lme4 package*' was used for the linear mixed-effects models, with random effects for individual participants. The primary fixed effects were the interaction between "Eating window" and "Exercise". The '*emmeans package*' was used to estimate marginal means with 95% confidence intervals and pairwise comparisons with Tukey's adjustment to control for multiple testing. The significance was assessed through p-values ($P<0.05$) and effect size and magnitude of the observed effects were calculated using the '*effectsize package*'.

3. Results

Seventeen participants with type 2 diabetes mellitus were recruited; fifteen completed the study, and fourteen (5 F, 9 M; HbA1c: 7.6 ± 1.0%, 60.0 ± 10.4 mmol/mol) were included in the analysis. The baseline characteristics are shown in **Table 1**, and baseline medications are presented in **Table S2**. One participant enrolled but did not start the study and thus was not randomised; one participant withdrew due to an unrelated illness after completing two conditions. There were no adverse events reported by participants throughout the study. One participant completed the study who was taking 3 OHAs which was unbeknownst to the authors until the analysis stage. As this was a protocol violation, this participant was not included in the analysis as per the CONSORT flow diagram **(Fig. S1)**.

There was no difference between the energy or macronutrient intake for the two days before each condition **(Table S6)**, and participants consumed the same meals during each condition (i.e., exercise conditions had a standardised snack after each meal). There were no differences between bedtime, wake time, time in bed, sleep duration, sleep latency, sleep efficiency, wake after sleep onset or wake bouts between conditions **(Table S7)** or in the daily step count two days before each condition (baseline).

Participants exercised at 56.4 ± 6.9% of VO_2peak (5.3 ± 0.8 km/h) during the exercise conditions (i.e., TRE + Ex and CON + Ex) with 0–4.5% inclination. There were no differences in step count between conditions for the total trial day or 2-h post-meal periods **(Table 2)**. There was an increase in the total daily step count during exercise conditions TRE + Ex (+5617 steps) and CON + Ex (+5853 steps) compared with the non-exercise (TRE and CON, respectively) conditions ($P<0.001$).

Table 1
Baseline characteristics of the participants with type 2 diabetes mellitus who were randomised and completed the four conditions for the study.

	All randomised (n = 16)	Included in the analysis (n = 14)
Age, y	56.1 ± 6.4	56.8 ± 5.4
Sex, n (%)		
Female	5 (31%)	5 (36%)
Male	11 (69%)	9 (64%)
Body mass, kg	97.3 ± 17.9	98.7 ± 18.7
Lean mass, kg	57.2 ± 10.9	57.5 ± 11.4
Fat mass, kg	40.8 ± 16.0	42.5 ± 16.5
Body fat, %	38.9 ± 7.9	39.5 ± 8.3
Height, cm	173.9 ± 9.3	174.1 ± 9.5
BMI, kg/m^2	32.2 ± 4.7	32.6 ± 4.9
MEQ-SA	56 ± 6	57 ± 6
Medication, n (%)		
None	3 (19%)	3 (21%)
1 OHA	7 (44%)	6 (43%)
2 OHAs	5 (31%)	5 (36%)
3 OHAs	1 (6%)	0 (0%)
Medication type, n (%)		
Biguanide	6 (38%)	5 (36%)
SGLT2i	0 (0%)	0 (0%)
DPP4i	1 (6%)	1 (7%)
Biguanide + SGLT2i	4 (25%)	4 (29%)
Biguanide + DPP4i	1 (6%)	1 (7%)
Biguanide + SGLT2i + DPP4i	1 (6%)	0 (0%)
HbA1c, %	7.6 ± 0.9	7.6 ± 1.0
HbA1c, mmol/mol	59.2 ± 10.2	60.0 ± 10.4
HOMA-IR	–	3.2 ± 1.9

Data presented as n (%) or mean ± SD. BMI, body mass index, OHA, oral hypoglycaemic agents. MEQ-SA, Morningness-Eveningness Questionnaire (score ≤41 indicates evening type and ≥59 indicates morning type). DPP4i, dipeptidyl peptidase IV inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors; HOMA-IR, homeostatic model assessment and insulin resistance (>2.9 indicates insulin resistance).

Table 2
Mean ± SD step count (n) per condition from the ActivPAL activity monitors.

	CON	CON + Ex	TRE + Ex	TRE
	n = 11	*n = 13*	*n = 11*	*n = 11*
Total trial day	3198 ± 1166	8862 ± 1491	9097 ± 1652	3481 ± 1508
2-h post breakfast	171 ± 53	1994 ± 197	1969 ± 175	71 ± 108
2-h post lunch	124 ± 77	1912 ± 267	1981 ± 205	141 ± 104
2-h post dinner	181 ± 178	2095 ± 272	2055 ± 150	149 ± 94
One day prior (baseline)	7982 ± 2621	6200 ± 2167	6759 ± 2634	6891 ± 3006
Two days prior (baseline)	6302 ± 2651	6411 ± 3319	6384 ± 2507	5689 ± 4197

Note: The number of participants differs due to missing days in which the monitors were dislodged, no data was recorded, or errors occurred in the downloading data process.

The patterns of plasma and interstitial glucose, insulin, and nocturnal glucose concentrations are presented in Fig. 2**A, 2D, 2G and 2 J**. There was no effect of eating window or exercise on plasma glucose 14-h AUC (Fig. 2**B**). A main effect of eating window on plasma glucose 14-h iAUC was observed **(**Fig. 2**C),** but there were no exercise or interaction effects. Post hoc analysis revealed that plasma glucose 14-h iAUC was lower in CON + Ex compared with TRE + Ex (−15 mmol/L, 95% CI: −30 to −1 mmol/L, P=0.03) and TRE (−17 mmol/L, −31 to −2 mmol/L, P=0.01). Moreover, a main effect of eating window on the interstitial glucose 14-h AUC (6 mmol/L, −2 to 14 mmol/L, P=0.01; Fig. 2**E**) and interstitial glucose 14-h iAUC (10 mmol/L, 1 to 19, P=0.03; Fig. 2**F**) was

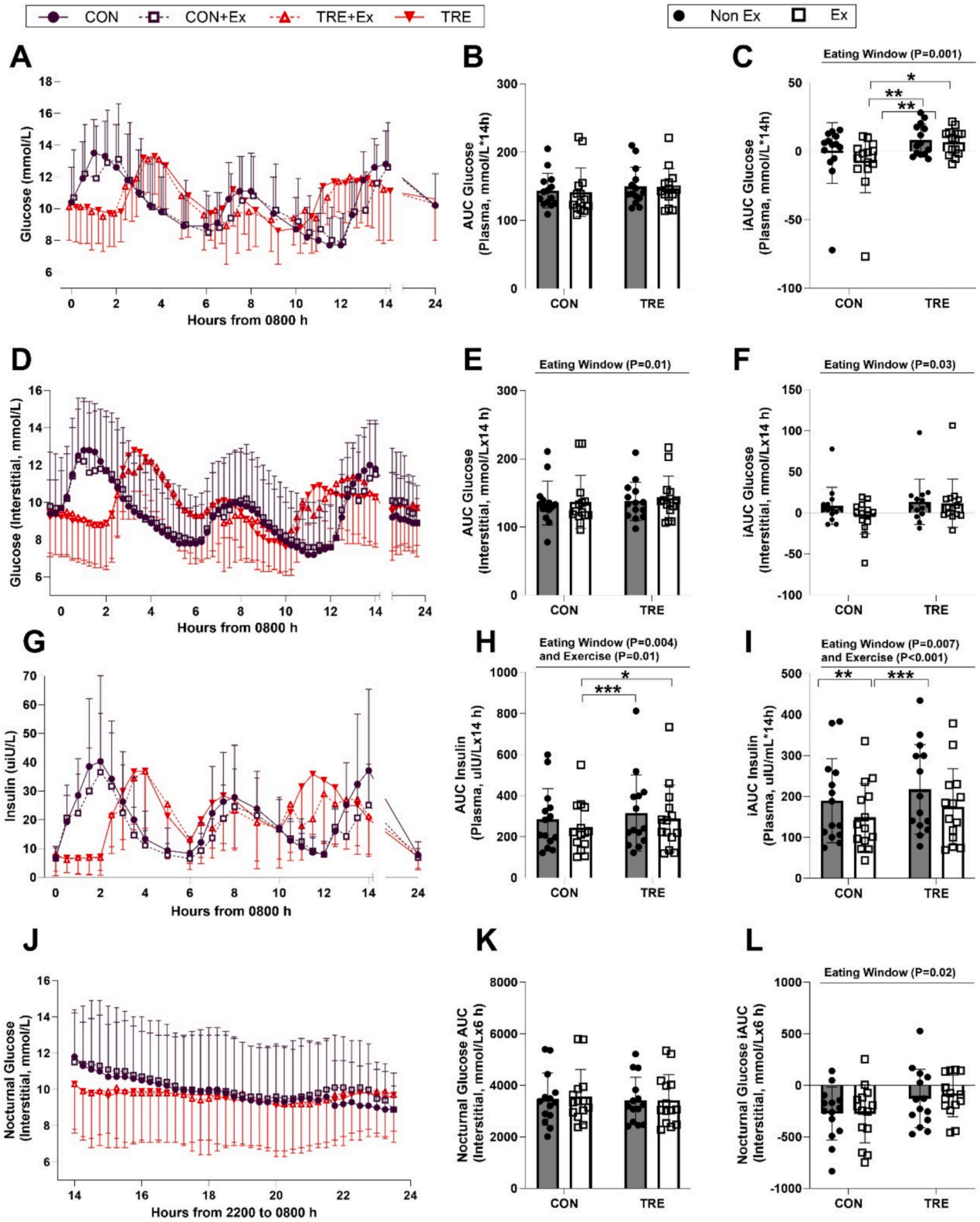

Fig. 2. Mean trial day plasma glucose, mean insulin, interstitial glucose, and nocturnal glucose concentrations (A, D, G, J), AUC plasma glucose, insulin, interstitial glucose and nocturnal glucose concentrations (B, E, H, K), and iAUC plasma glucose, insulin, interstitial glucose and nocturnal glucose concentrations (C, F, I, L) between conditions in people with type 2 diabetes mellitus. CON, Extended eating window (purple circles; black circles); CON + Ex, Extended eating window + Exercise (purple border, white filled circles; white squares); TRE, Time-restricted eating (red border, white filled triangles; black circles); TRE + Ex, Time-restricted eating + Exercise (red triangles; white squares; Exercise, 15 min at ~60% VO_2peak). Data presented as Mean ± SD;*P<0.05, **P<0.01, ***P<0.001. Figure created in GraphPad Prism. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observed.

There was a main effect of the eating window (P=0.004) and exercise (P=0.01) on insulin 14-h AUC, where CON + Ex was lower compared with TRE and TRE + Ex (−75 uIU/Lx14 h, 95% CI: −126 to −25 uIU/Lx14 h, P=0.002; −51 uIU/Lx14 h, −101 to −1 uIU/Lx14 h, P=0.04; Fig. 2**H**). There was a main effect of the eating window (P=0.007) and exercise (P <0.001) on lowering insulin 14-h iAUC, where CON + Ex and TRE + Ex showed lower 14-h iAUC compared with the non-exercise conditions (CON + Ex vs CON: −46 uIU/Lx14 h; −83 to −8 uIU/Lx14 h, P=0.01; TRE + Ex vs TRE: −40 uIU/Lx14 h, −77 to −2 uIU/Lx14 h, P=0.03; Fig. 2**I**). No difference between conditions in nocturnal (0000 to 0600 h) interstitial glucose 6-h AUC was observed (Fig. 2**K**). However, the eating window lowered nocturnal interstitial glucose 6-h iAUC (P=0.02; Fig. 2**L**).

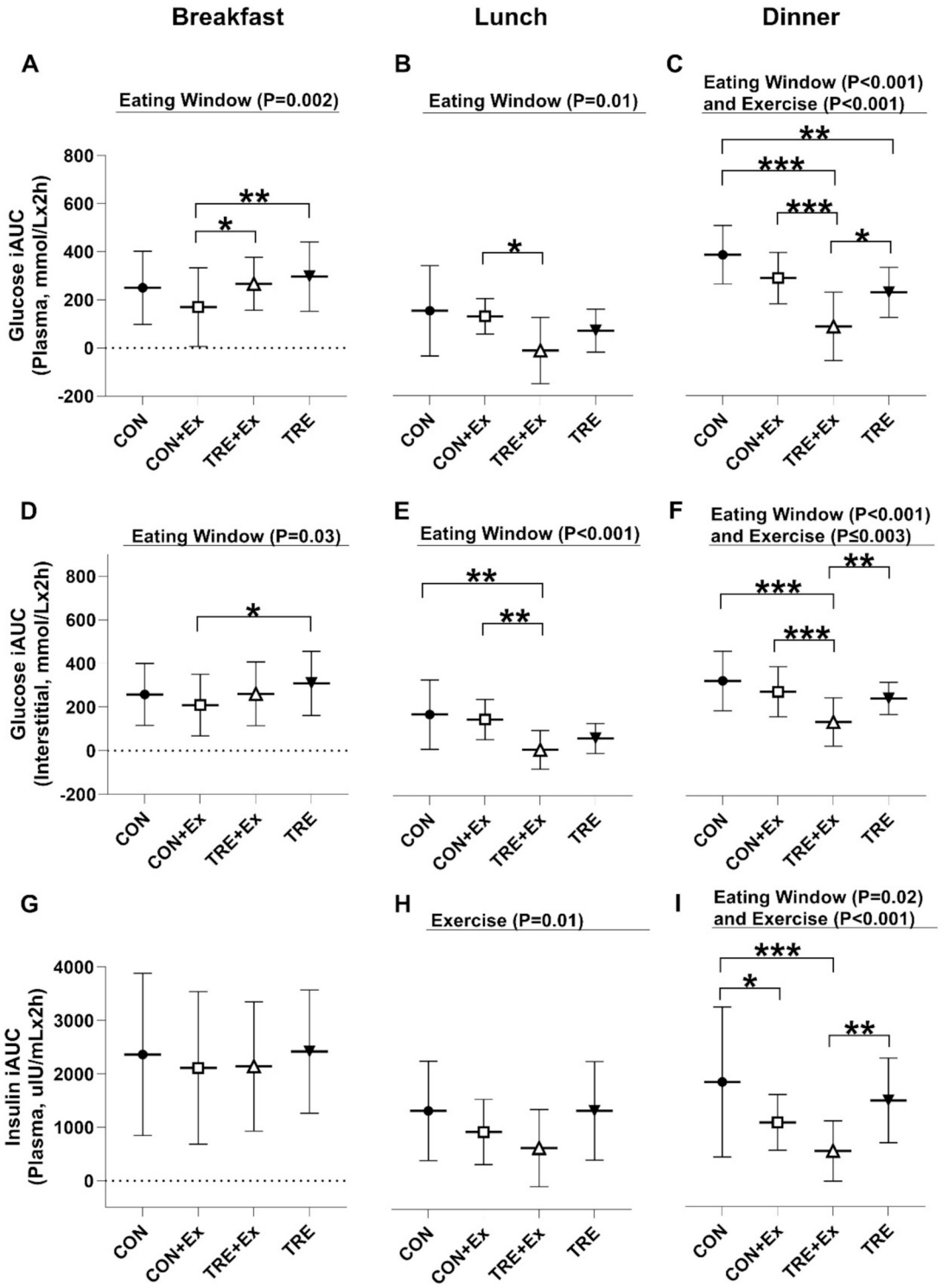

Fig. 3. Postprandial breakfast 2-h iAUC plasma glucose, interstitial glucose and insulin for breakfast (A, D, G), lunch (B, E, H) and dinner (C, F, I) between conditions in people with type 2 diabetes mellitus. CON, black circle; CON + Ex, white square; TRE + Ex, white triangle; TRE, upside-down black triangle. Main effects and Tukey post-hoc analysis: *P<0.05, **P<0.01, ***P<0.001. Figure created in GraphPad Prism.

There was no eating window or interaction effects on NEFA 14-h AUC. However, exercise showed an effect (P=0.006) where TRE was lower compared with CON + Ex (−0.68 mmol/L; 95% CI: 0.07 to 1.29 mmol/L; P=0.006; **Fig. S2E).** There were no effects of the eating window, exercise or interaction on NEFA 14-h iAUC. There were no effects of the eating window, exercise or interaction on triglycerides (TAG) 14-h AUC or 14-h iAUC (**Fig. S2F**).

There was a main effect of the eating window on the post-breakfast plasma (P=0.002) and interstitial (P=0.03) glucose 2-h iAUCs, where post hoc analysis showed that CON + Ex was lower than TRE + Ex (Plasma: −101 mmol/Lx2h, 95% CI: −197 to −5 mmol/Lx2h, P=0.04) and TRE (Plasma: −123 mmol/Lx2h, 95% CI: −219 to −27 mmol/Lx2h, P=0.008; Interstitial: −130 mmol/Lx2h, −248 to −13 mmol/Lx2h, P=0.02; Fig. 3**A and 3D)**, with no exercise or interaction effects. There were no effects of the eating window, exercise or interaction in the post-breakfast insulin 2-h iAUC (Fig. 3**G).**

There was a main effect of the eating window in the post-lunch plasma and interstitial glucose 2-h iAUC (P=0.01 and P<0.001; Fig. 3**B and 3E**), where TRE + Ex was lower compared with CON + Ex (Plasma: −131 mmol/Lx2h, 95% CI: −260 to −2 mmol/Lx2h, P=0.04; Interstitial: −142 mmol/L; 95% CI: −241 to −43 mmol/L; P=0.003). Additionally, TRE + Ex lowered the interstitial glucose 2-h iAUC compared with CON (−141 mmol/Lx2h, 95% CI: −245 to −37 mmol/Lx2h, P=0.004), with no exercise or interaction effects. There was a main effect of exercise decreasing post-lunch insulin 2-h iAUC (P = 0.01; Fig. 3**H**), but no effect of eating window or interaction.

There were main effects of the eating window and exercise lowering the post-dinner plasma (both P<0.001) and interstitial glucose 2-h iAUC (both P≤0.003), but no interaction effect (Fig. 3**C and 3F)**. Post hoc analysis showed that post-dinner 2-h iAUC was lower in TRE + Ex compared with TRE (Plasma: −141 mmol/Lx2h, 95% CI: −247 to −15 mmol/Lx2h, P=0.02; Interstitial: −115 mmol/Lx2h, 95% CI: −211 to −19 mmol/Lx2h, P=0.01), CON (Plasma: −301 mmol/Lx2h, 95 %CI: −430 to −172 mmol/Lx2h, P<0.001; Interstitial: −190 mmol/Lx2h, 95% CI: −289 to −92 mmol/Lx2h, P<0.001) and CON + Ex (Plasma: −208 mmol/Lx2h, 95% CI: −84 to −331 mmol/Lx2h, P<0.001; Interstitial: −146 mmol/Lx2h, 95% CI: −52 to −239 mmol/Lx2h, P=0.001). Moreover, plasma glucose 2-h iAUC was lower in TRE compared with CON (Plasma: −160 mmol/Lx2h, 95% CI: −31 to −288 mmol/Lx2h, P=0.01), with no effects on interstitial glucose 2-h iAUC. There was a main effect of the eating window (P=0.02) and exercise (P<0.001) in reducing the post-dinner insulin 2-h iAUC in the exercise conditions compared with non-exercise conditions (CON + Ex vs CON: -788 uIU/mLx2h, 95 %CI: −1463 to −92 uIU/mLx2h, P=0.02; TRE + Ex vs TRE:-920 uIU/mLx2h, 95% CI: −1604 to −236 uIU/mLx2h, P=0.01) and TRE + Ex compared with CON (−1280 uIU/mLx2h, 95% CI: −1982 to −578 uIU/mLx2h, P<0.001; Fig. 3**I**), but no interaction effects.

There was a main effect of time on the expression of several genes related to glucose uptake (IRS2), the circadian clock (PER1, PER2, and RORA), and oxidative stress (SOD1) **(Fig. S3A-E).** A main effect of eating window on FOXO3 expression was observed, and post hoc analysis revealed that FOXO3 expression was lower at 1600 h in TRE compared to CON (P=0.047). A time × group interaction effect was observed for BMAL expression **(Fig. S3A).** However, post hoc analysis did not reveal differences in BMAL expression between conditions at any specific timepoint. There was no effect of acute TRE on the expression of other genes measured **(Fig. S3).**

There was a main effect of eating window on both systolic and diastolic BP (SBP, DBP, both P<0.001), with an interaction only on SBP (P=0.008). TRE + Ex lowered SBP compared with TRE (−2 mmHg; 95% CI: −4 to 0, P=0.03), CON (−3 mmHg; 95% CI: −5 to −1, P=0.01) and CON + Ex (−3 mmHg; 95% CI: −1 to −6, P<0.001). TRE + Ex lowered DBP compared with CON + Ex (−1 mmHg; 95% CI: 0 to −3, P=0.009). There was an effect of the eating window, exercise and interaction (all P<0.001) on HR, where all conditions with exercise had higher HR compared with the non-exercise condition (i.e., TRE + Ex was higher than TRE (+7 bpm, 95% CI: 5 to 8 bpm, P<0.001); CON + Ex was higher than CON (+3 bpm, 95% CI: 1 to 5 bpm, P<0.001); **Fig. S4**).

There were main effects of the eating window (P<0.001), exercise (P = 0.001), time (P < 0.001) and eating window × time interaction (P<0.001) on rates of CHO oxidation. TRE + Ex had higher CHO oxidation at the pre-lunch timepoint (+0.07 g/min, 95% CI: 0.35 to 0.14 g/min, P=0.002), post-lunch timepoint (+0.09 g/min, 95% CI: 0.41 to 0.20 g/min, P<0.001) and post-dinner timepoint (+0.08 g/min, 95% CI: 0.37 to 0.15 g/min, P=0.001) compared with CON + Ex, but there were no interaction effects on CHO oxidation rates. There were main effects of eating window (P<0.001), exercise (P=0.03), time (P<0.001) and eating window × time interaction (P<0.001) on rates of fat oxidation. There was an effect post-lunch where fat oxidation was higher in CON + Ex (+0.03 g/min, 95% CI: 0.16 to 0.37 g/min, P<0.001) compared with TRE + Ex and in CON + Ex (+0.03 g/min, 95% CI: 0.18 to 0.40 g/min, P<0.001) compared with TRE **(Fig. S5).**

4. Discussion

This study is the first to determine the acute effects (14-h) of combining TRE with exercise on glucose and insulin concentrations in a laboratory setting, where diet and exercise were controlled. Whilst a 4-h reduction in eating window induced a different pattern of glucose and insulin concentrations, there was no difference in 14-h plasma glucose AUC between 8-h TRE and a 12-h eating window with or without exercise. Furthermore, we show that post-meal exercise (15 min walk, ~2000 steps) after each main meal reduced daily insulin AUC. Whilst exercise recommendations appear in clinical guidelines for type 2 diabetes mellitus [1,32,33] the timing in relation to meals is not stipulated. Although there was little benefit of TRE on lowering the insulin 14-h AUC, other studies of longer duration (i.e., five to twelve weeks) have demonstrated that TRE improves insulin sensitivity in people with or at risk of type 2 diabetes mellitus [16,34,50].

Despite our participants consuming the same meals during the trial, there were different post-prandial responses between conditions, especially at lunch (second) and dinner (third). TRE lowered post-lunch and post-dinner glucose 2-h iAUC, likely due to the elevated insulin concentrations with shorter times between meals. As previously reported [20,23,35,36], post-meal exercise lowered the post-lunch and dinner insulin 2-h iAUC. Besides fasting glucose and HbA_{1c}, the 2-h post-prandial blood glucose is an indicator of blood glucose control and an independent risk factor for cardiovascular disease in people with and without type 2 diabetes mellitus [37–39]. As such, attenuating post-prandial glucose peaks after each meal can reduce daily glycaemic variability, optimising the daily oscillations and glycaemic management [35,40,41]. We observed lower glucose 2-h iAUC post-breakfast in the extended eating condition combined with exercise compared with TRE with and without exercise. Other studies have shown that delaying breakfast can improve blood glucose [42]. As both meals and exercise were rigorously controlled, participants could not voluntarily accumulate a greater step count before a mid-morning or delayed breakfast, as we have previously observed [11]. Thus, the beneficial effects of TRE for people with type 2 diabetes mellitus may be more related to the amount of physical activity prior to the meals than the timing *per se*. Additionally, TRE protocols may modify other behaviours (i.e., exercise before eating [43] or meal quality/quantity [44]).

Short-term (four days) TRE has been shown to induce changes in the expression of genes in whole blood related to glucose uptake, the circadian clock, longevity, and autophagy [29]. Furthermore, a single bout of breakfast skipping induces changes in postprandial expression of several clock genes in whole blood in healthy individuals and people with type 2 diabetes mellitus [44]. These findings suggest that there is a tightly controlled feedback loop between meal timing and a wide range of physiological systems. We found little effect of TRE on a range of selected gene expressions. It is difficult to reconcile the differences between our findings and those of previous studies, although they may be

related to differences in the population studied (i.e., people with overweight and obesity vs. healthy individuals vs. people with type 2 diabetes mellitus), differences in the duration of TRE (i.e., four days vs. 24-h), or differences in the sample collection timepoints between studies.

In the present study, TRE combined with post-meal exercise lowered SBP and DBP compared with a 12-h eating window combined with post-meal exercise. Consistent with our findings, 14 weeks of 8-h TRE has been shown to lower BP in males with obesity compared to >12 h window [14]. Sleep quality and duration are independent risk factors for glycaemic control in people with type 2 diabetes mellitus [45–47]. Therefore, strategies for improving nocturnal blood glucose may improve sleep health and result in positive outcomes for type 2 diabetes mellitus management [45]. TRE has been shown to lower nocturnal glucose concentrations [42] and improve sleep quality [44,49]. In this study, TRE lowered nocturnal interstitial 6-h iAUC but had no impact on sleep outcomes, which may be related to participants having a limited time to sleep due to returning to the lab at 0800 h the following day.

5. Strengths and limitations

In the current investigation, all meals the evening before and during the trials were standardised, allowing the effects of meal and exercise timing to be assessed independently. TRE did not result in reductions in fasting glucose levels, suggesting that a longer intervention is required to obtain benefits from TRE. Whilst examining the acute effect of TRE helps understand the daily regulation of blood glucose, the acute modification of the eating window with post-meal exercise bouts may need to be implemented consistently for a longer time frame (i.e., several days to weeks) to elicit an effect on fasting glucose and total AUC.

6. Conclusion

Post-meal exercise had a potent effect on lowering insulin 14-h AUC, whereas neither 8-h TRE nor exercise altered 14-h blood glucose compared with a 12-h extended eating window. TRE had the greatest impact on lowering post-prandial blood glucose. Future work should focus on the long-term effects of TRE combined with exercise for improving glucose management in people with type 2 diabetes mellitus.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contribution statement

APBG was involved in the conduct of the study as well as the analysis and interpretation of the results. **RH** and **BER** were involved in the design and conduct of the study. **SB, NT, BA,** and **KJ** were involved in the conduct of the study and sample analysis. **RJ** and **SLH** were involved in the analysis and interpretation of the results. **EBP** was involved in the conception, design, conduct, analysis and interpretation of the results. **JAH** and **BLD** were involved in the conception, design, and interpretation of the results. **APBG** wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. **EBP** is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Clinical Trial Registration

Australia New Zealand Clinical Trial Registry, ACTRN12619001222134

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.112081.

Data availability

Data will be made available on request.

All data supporting the findings of this study are available within the paper and electronic supplementary material. Data are available on request from the authors

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