Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans

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Objective: Eating earlier in the daytime to align with circadian rhythms in metabolism enhances weight loss. However, it is unknown whether these benefits are mediated through increased energy expenditure or decreased food intake. Therefore, this study performed the first randomized trial to determine how meal timing affects 24-hour energy metabolism when food intake and meal frequency are matched.

Methods: Eleven adults with overweight practiced both early time-restricted feeding (eTRF) (eating from 8 AM to 2 PM) and a control schedule (eating from 8 AM to 8 PM) for 4 days each. On the fourth day, 24-hour energy expenditure and substrate oxidation were measured by whole-room indirect calorimetry, in conjunction with appetite and metabolic hormones.

Results: eTRF did not affect 24-hour energy expenditure (Δ = 10 ± 16 kcal/d; P = 0.55). Despite the longer daily fast (intermittent fasting), eTRF decreased mean ghrelin levels by 32 ± 10 pg/mL (P = 0.006), made hunger more even-keeled (P = 0.006), and tended to increase fullness (P = 0.06-0.10) and decrease the desire to eat (P = 0.08). eTRF also increased metabolic flexibility (P = 0.0006) and decreased the 24-hour nonprotein respiratory quotient (Δ = -0.021 ± 0.010; P = 0.05).

Conclusions: Meal-timing interventions facilitate weight loss primarily by decreasing appetite rather than by increasing energy expenditure. eTRF may also increase fat loss by increasing fat oxidation.

Obesity (2019) 27, 1244-1254. doi:10.1002/oby.22518

Introduction

The circadian system orchestrates metabolism in a 24-hour cycle, giving rise to rhythms in energy expenditure (1,2), appetite (3-6), insulin sensitivity (7-9), and other metabolic processes (7). Many of these processes, including insulin sensitivity (7-9) and the thermic effect of food (TEF) (10-12), peak in the morning or around noontime. Increasingly, studies in both rodents and humans have shown that eating out of sync with these circadian rhythms (by eating during the biological night) promotes weight gain and metabolic dysfunction (13-17).

Conversely, eating in sync with circadian rhythms by eating early in the daytime appears to reduce body weight and improve metabolic health. In a seminal randomized controlled trial, Jakubowicz et al. (18) tested whether following the popular adage of “eating breakfast like a king, lunch like a prince, and dinner like a pauper” affects weight loss. They found that women randomly assigned to eat a large breakfast lost 5.1 kg more weight in a 12-week period than those who were prescribed an isocaloric diet but ate a small breakfast (8.7 ± 1.4 kg vs. 3.6 ± 1.5 kg, respectively) (18). Since then, several other interventional and cohort studies have reported that shifting food intake to earlier during the daytime increases weight loss (19-24).

However, the mechanism(s) driving these weight loss effects are unknown. Some studies have suggested that the primary mechanism is decreased appetite. Limiting food intake to an 8- to 11-hour period...
during the daytime (20,23,25) and eating a large breakfast and small dinner (18,26,27) decrease appetite and/or food intake in humans, with only one trial reporting an exception (6). Other studies have suggested that the primary mechanism is increased energy expenditure. In rodents, eating within an 8-hour period early in their activity period increased 24-hour energy expenditure, in parallel with changes reflecting enhanced brown adipose tissue thermogenesis (28). In addition, TEF (the energy expended in metabolizing and storing ingested calories) is higher in humans in the morning because of the circadian system (10-12), so eating earlier in the daytime should increase energy expenditure. Indeed, one trial in Spanish adults reported that shifting the timing of lunch from 4:30 to 1:00 PM increased postprandial energy expenditure; however, the measurements were performed over only a 4-hour period (29). A more recent three-arm study in humans found that skipping dinner increased 24-hour energy expenditure by 91 kcal/d (30). However, the order of the control arm was not randomized, food intake and meal frequency were not matched among groups, and physical activity (measured via step count) was nonsignificantly higher by 10% in the dinner-skipping arm.

We therefore performed the first randomized controlled feeding trial to determine whether meal timing affects 24-hour energy expenditure under conditions of matched food intake and meal frequency. We compared a form of meal timing called early time-restricted feeding (eTRF) (31) with eating at typical American mealtimes (32). eTRF combines two different meal-timing strategies: (1) shifting the majority of food intake to earlier in the daytime to align with circadian rhythms in metabolism and (2) daily intermittent fasting (time-restricted feeding, defined here as fasting for ≥14 h/d); eTRF is tantamount to eating dinner in the midafternoon and fasting for the rest of the day (31). The primary end point was 24-hour energy expenditure, whereas secondary end points included substrate oxidation, subjective appetite, and metabolic hormones. Based on preclinical studies, we hypothesized that eTRF would increase 24-hour energy expenditure.

Methods

Participants

The trial was conducted at Pennington Biomedical Research Center (PBRC) (Baton Rouge, Louisiana), approved by its institutional review board, and preregistered at ClinicalTrials.gov (identifier: NCT02247076). Participants were recruited between November 2014 and August 2016. Generally healthy adults aged 20 to 45 years old were eligible to participate if they had BMI between 25 and 35 kg/m² (inclusive), body weight between 68 and 100 kg, a regular bedtime between 9:30 PM and 12:00 AM, and a regular menstrual cycle (for women). The exclusion criteria are provided in the online Supporting Information. All participants provided written informed consent and received a stipend for their participation.

Study design

This study was designed as a randomized, crossover, isocaloric, controlled feeding trial. Participants were randomly assigned to follow either the control schedule (eating between 8:00 AM and 8:00 PM; 12-hour daily eating period), which is similar to the median reported breakfast and dinner times for American adults (32), or an eTRF schedule (eating between 8:00 AM and 2:00 PM; 6-hour daily eating period) for 4 days and then to crossover to the other arm after a 3.5- to 5-week washout period. A 6-hour daily period was selected both to maximize differences relative to the control arm and because it was hypothesized to be the smallest...
eating window that could be sustained long term by humans. On days −3 to 3, participants were required to go to bed between 9:30 PM and 12:00 AM and to maintain a regular bedtime. On days 1 to 2 of each arm, participants followed either the control schedule or the eTRF schedule on their own (Figure 1). On days 3 to 4, participants continued to follow their assigned schedule but ate only food provided by study staff while under supervision. Meals for the control schedule were served at 8:00 AM, 2:00 PM, and 8:00 PM, whereas meals for the eTRF schedule were served at 8:00 AM, 11:00 AM, and 2:00 PM. The three daily meals (50% carbohydrate, 35% fat, and 15% protein) were matched across arms and were designed to meet weight maintenance energy requirements under sedentary conditions. To do so, we used an energy expenditure equation based on weight, height, age, sex, and ethnicity that was developed for use in 24-hour respiratory chamber studies (33). This equation was used as is on day 4 but was multiplied by an activity factor of 1.11 for day 3 to account for greater physical activity in free-living conditions. No other food or beverages (except for water and noncaffeinated, nonalcoholic drinks) were allowed. To ensure compliance, participants ate their three provided meals in the PBRC kitchen on day 3 but were otherwise in an outpatient setting. On day 4, participants completed a 24-hour inpatient stay in a respiratory chamber, with concomitant measurement of appetite and metabolic hormones. All women performed respiratory chamber testing during the luteal phases of their menstrual cycle. Neither the participants nor the study staff were blinded.

Respiratory chamber
To measure energy expenditure and substrate oxidation, participants resided in a respiratory chamber for 24 hours (34) starting at 7:00 AM on day 4. While in the chamber, participants consumed three identical isocaloric meals (consisting of a strawberry yogurt smoothie with whey protein and skim milk and a peanut butter and jelly sandwich), following the same schedule as on day 3 (Figure 1B). Participants were required to lay supine and motionless from 7:00 to 8:00 AM for measurement of resting energy expenditure and from 8:45 to 9:30 AM, 11:45 AM to 12:30 PM, 2:45 to 3:30 PM, and 8:45 to 9:30 PM for measurement of TEF (Figure 1). Participants slept from approximately 10:30 PM to 1:30-2:29 AM, 2:30-3:29 AM, for the daytime (8:00 AM -7:59 PM), and were analyzed for the whole 24-hour period, in hourly increments (e.g., (lights off) to 6:30 AM (lights on). Energy expenditure was calculated between 2:00 and 4:59 AM for all minutes when physical activity was measured using the Weir equation with urinary nitrogen excretion data. Data were analyzed for the whole 24-hour period, in hourly increments (e.g., 1:30-2:29 AM, 2:30-3:29 AM), for the daytime (8:00 AM-7:59 PM), and for the nighttime (8:00 PM-7:59 AM). Sleeping energy expenditure was calculated between 2:00 and 4:59 AM for all minutes when physical activity, as measured by radar, was <1%. Resting energy expenditure was calculated as the average energy expenditure between 7:35 and 7:55 AM, whereas postprandial energy expenditure for the TEF calculation was measured during the period 60 to 85 minutes (a 25-minute period) following each meal. Because postprandial energy expenditure peaks at approximately 1 to 1.5 hours post meal and then steadily declines over the subsequent 5 to 6 hours, using only the value measured in the early postprandial period would overestimate TEF. Because data from Segal et al. (35) indicate that the mean incremental energy expenditure is approximately half the peak value, the area under the curve (AUC) for the TEF calculation was calculated as half the measured value times 6 hours. Percent physical activity within the chamber was quantified as the percent of the time in motion as measured by two radar motion detectors. Energy expenditure from spontaneous physical activity was calculated as the difference between total 24-hour energy expenditure and the y-intercept from the linear regression of energy expenditure versus the percentage of physical activity, using the data averaged in 15-minute intervals (34). Metabolic flexibility (the ability to switch between oxidizing different substrates) was defined as the difference between the maximum and minimum values of the nonprotein respiratory quotient (nPRQ) when averaged in 1-hour intervals.

Serum and urine chemistry
Blood was drawn for measurement of leptin, active ghrelin, peptide YY3-36 (PYY), and glucagon-like peptide 1 (GLP-1) in the fasting state at 8:00 PM on day 3 (evening draw) and immediately after exiting the chamber at approximately 7:30 AM on day 5 (morning draw). Assays were performed as described in the online Supporting Information. Mean values were derived by averaging together morning and evening values.

Subjective appetite and energy levels
Participants rated their hunger, desire to eat, capacity to eat, fullness, stomach fullness, energy levels, awareness, and perceived body temperature, using visual analog scales (VAS) (0- to 100-mm scale). The VAS survey was administered about every 3 hours for a total of six times: at 8:00 AM, 11:00 AM, 2:00 PM, 5:00 PM, 8:00 PM, and 10:30 PM. Surveys administered at the same time as a scheduled meal were filled out before participants ate the meal. Daily mean values of the eight indices were calculated as the AUC value divided by the measurement duration in hours, whereas the diurnal amplitude for each index was calculated as the difference between the maximum and minimum values.

Statistical methods
Statistical analyses were performed as two-tailed tests in SAS software (version 9.4; SAS Institute, Inc., Cary, North Carolina), with α=0.05. A power analysis indicated that 10 individuals were needed to have 80% power to detect an 80-kcal/d difference in 24-hour energy expenditure (the primary end point) based on unpublished data indicating a within-subjects SD of σ=79 kcal/d. Randomization was stratified by sex in blocks of four. Additional information on the randomization and missing data are provided in the online Supporting Information. Baseline data and the data for each arm are reported in the text as raw mean (SD), whereas the treatment effects or differences between arms (denoted as Δ) are reported as least squares mean±SEM. The treatment effects and associated P values were computed using linear mixed models with heterogeneous compound symmetry, with participants as the random effect and the treatment, period, sequence, and sex as fixed effects, using the Satterthwaite method for calculating degrees of freedom. Error bars in the figures are presented as SEM for visual clarity.

Results
Participant characteristics
A total of 331 adults were screened for the study, 18 participants were randomly assigned, and 11 participants completed the intervention (Figure 2). Of the seven participants who withdrew, four withdrew for family or personal reasons, two withdrew because of scheduling conflicts, and one was withdrawn for an unrelated medical reason (life-altering injury from a motor vehicle crash). The 11 adults (7 men and 4 women; 64% African American, 27% white, and 9% other race) who completed the intervention had a mean (SD) age of 32 (7) years, mean BMI of 30.1 (2.7) kg/m², mean fasting glucose of 92 (5) mg/dL, and mean blood pressure of 112 (9)/77 (5) mm Hg.
Energy balance
Each of the 10 completers ate the same amount of food while following the two meal-timing schedules (2,180 [270] kcal/d), and participants were 100% compliant, with no weigh-backs in either arm ($\Delta = 0 \pm 0$ kcal/d; $P = 1.00$). Although we intended to feed participants eucaloric diets, participants were less active in the chamber than we expected (physical activity level of 1.16 [0.10]), likely because of the mandated rest periods for measuring TEF, and consequently were in positive energy balance on both the eTRF and control schedules (270 [109] vs. 283 [125] kcal/d; $\Delta = -11 \pm 16$ kcal/d; $P = 0.52$). Participants’ mean body weights upon entering the respiratory chamber were the same in both arms (89.8 [8.8] vs. 90.1 [8.9] kg; $P = 0.32$). However, while in the chamber, participants in the eTRF arm had a $\Delta = 0.2 \pm 0.1$-kg decrease in weight relative to those in the control arm ($P = 0.05$), likely because of glycogen depletion from the extended daily fasting.

Energy expenditure
Energy balance data are provided in the online Supporting Information. Figure 3A shows the hourly values of energy expenditure for the two eating schedules. Relative to the control schedule, eTRF increased energy expenditure for a 6-hour period from 10:30 AM to 4:29 PM.

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**Figure 2** Participant flow diagram. eTRF, early time-restricted feeding.
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(P ≤ 0.007) but decreased energy expenditure across a 4-hour period from 7:30 to 11:29 pm (P ≤ 0.01) and a 2-hour period from 1:30 to 3:29 am (P ≤ 0.003). As shown in Figure 3B, most of these differences could be attributed to changes in TEF. eTRF increased TEF following the second (P = 0.0008) and third meals (P ≤ 0.0001) of the day but not the first meal (P = 0.93), translating into a Δ = 2.4% ± 0.7% absolute increase in mean TEF values (P = 0.003) or a Δ = 0.011 ± 0.011 kcal/min increase in postprandial energy expenditure (P = 0.0003). In contrast, resting energy expenditure (P = 0.57) and spontaneous physical activity (180 [82] vs. 168 [90] kcal/d; Δ = 11 ± 9 kcal/d; P = 0.23) were unaffected (Figure 3C). As a result, daytime energy expenditure was higher in the eTRF arm by Δ = 56 ± 15 kcal per 12 hours (P = 0.003); however, this was offset by a decline in energy expenditure by Δ = −46 ± 6 kcal per 12 hours during the nighttime (P ≤ 0.0001) and while sleeping (P = 0.01). In aggregate, although eTRF did increase 24-hour energy expenditure in 8 of 10 participants (distribution of individual values shown in Supporting Information Figure S1), eTRF did not significantly affect 24-hour energy expenditure (1,910 [285] vs. 1,897 [266] kcal/d; Δ = 10 ± 16 kcal/d; P = 0.55).

**Substrate oxidation**

As shown in Figure 4, eTRF increased 24-hour protein oxidation by Δ = 13 ± 4 g/d (85 [15] vs. 71 [11] g/d; P = 0.009). Because eTRF caused some participants’ respiratory quotient values to drop below 0.71 at nighttime and because we did not measure ketone excretion, we could not directly quantify fat oxidation, and we instead report the npRQ. eTRF decreased the npRQ nearly continuously across a 12-hour period from 8:30 pm to 8:29 am (all P ≤ 0.08 with only two exceptions; Figure 5A). In contrast, eTRF increased the npRQ for only 2 hours in the middle of the day (12:30-2:29 pm; P ≤ 0.001). In aggregate, eTRF decreased the 24-hour npRQ by Δ = −0.021 ± 0.010 (0.776 [0.047] vs. 0.799 [0.049];

![Figure 3](image-url)
These differences were driven by a lower npRQ at nighttime (0.729 [0.050] vs. 0.778 [0.050]; Δ = −0.046 ± 0.010; P = 0.0007), while sleeping (Δ = −0.031 ± 0.013; P = 0.03), and while fasting in the morning (Δ = −0.036 ± 0.014; P = 0.02). There were no differences in the daytime npRQ (P = 0.72) or the postprandial npRQ following any of the three meals (P ≥ 0.71; data not shown). As shown in Figure 5C, the decrease in the npRQ at nighttime in the eTRF arm translated into greater 24-hour metabolic flexibility (0.209 [0.046] vs. 0.166 [0.048]; Δ = 0.041 ± 0.009; P = 0.0006).

**Metabolic hormones**

As shown in Figure 6, eTRF decreased morning levels of active ghrelin (Δ = −43 ± 15 pg/mL; P = 0.009), leptin (Δ = −4 ± 1 ng/mL; P = 0.01), and GLP-1 (Δ = −0.8 ± 0.3 pmol/mL; P = 0.008) but did not affect PYY (P = 0.25). In the evening, eTRF tended to decrease active ghrelin levels.
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(Δ = −22 ± 12 pg/mL; P = 0.09) and increase PYY levels (Δ = 17 ± 6 pg/mL; P = 0.02) but did not affect leptin (P = 0.18) or GLP-1 (P = 0.36). In aggregate, eTRF lowered mean levels of ghrelin by Δ = −32 ± 10 pg/mL (P = 0.006) and tended to decrease mean values of leptin (Δ = −5 ± 2 ng/mL; P = 0.07).

Appetite and energy level by VAS

Temporal data on subjective appetite, energy levels, awakeness, and perceived body temperature are provided in Figure 7, and the daily mean, maximum, and minimum values for each index are displayed in Figure 8. eTRF altered temporal patterns of all eight indices. Most notably, eTRF decreased several facets of appetite in the middle of the day (11:00 AM-5:00 PM; P ≤ 0.05) but increased all five appetite indicators late in the evening at bedtime (10:30 PM; all P ≤ 0.007). eTRF did not affect appetite at breakfast (8:00 AM; P = 0.09 for capacity to eat, but P ≥ 0.39 for all other indices) or in the middle of the evening (8:00 PM; P ≥ 0.27). In aggregate, eTRF tended to decrease the mean desire to eat by Δ = −5 ± 2 mm (P = 0.08) and tended to slightly increase mean fullness (Δ = 3 ± 2 mm; P = 0.10) and stomach fullness (Δ = 3 ± 2 mm; P = 0.06) while awake. It also reduced or tended to reduce the diurnal amplitudes in hunger (Δ = −10 ± 3 mm; P = 0.006) and the desire to eat (Δ = −9 ± 5 mm; P = 0.09), respectively. All other daily mean values and diurnal amplitudes (data not shown) were unaffected (P ≥ 0.14).

Adverse events

There was only one adverse event possibly related to the study intervention: one participant (who later withdrew from the trial) reported nausea and vomiting while on the control schedule.

Discussion

Eating earlier in the daytime to align with circadian rhythms in metabolism appears to reduce body weight (18-23). However, the mechanisms behind these effects in humans are unknown. Some trials have implied that the primary mechanism is increased energy expenditure (18,21,22,29,30) (conferring a metabolic advantage), whereas others have reported decreased food intake and/or appetite (18,20,25-27). However, prior studies have measured food intake by self-report or have had other limitations, such as not measuring energy expenditure over a 24-hour period.

We therefore conducted the first mechanistic trial to determine the effects of meal timing on 24-hour energy metabolism while matching both food intake and meal frequency to the control schedule. In contrast to rodent studies (28), we found that meal timing did not substantially increase 24-hour energy expenditure in humans. There were temporal differences in energy expenditure, but they arose mostly at times when meals were served in one study arm but not in the other, suggesting that such differences arose from asymmetries in whether participants were in absorptive versus postabsorptive states. We speculate that eTRF may have increased energy expenditure in rodents but not in humans because (1) brown fat activity is a greater fraction of energy expenditure in rodents than humans; (2) the rodents following eTRF had increased food-seeking behaviors, which boosted their activity energy expenditure; (3) the rodents’ timing and duration of sleep differed between the eTRF and control groups; and/or (4) rodent energy expenditure was normalized by body weight rather than by fat-free mass and fat mass, as recommended (36).

Our data are in agreement with a prior study finding that skipping breakfast did not negatively affect 24-hour energy expenditure (37) but are in

Figure 6 Early time-restricted feeding (eTRF) decreased fasting levels of (A) active ghrelin, (C) leptin, and (D) glucagon-like peptide 1 (GLP-1) in the morning, whereas it tended to (A) decrease active ghrelin levels and (B) increase peptide YY3-36 (PYY) levels in the evening. When averaged together, eTRF lowered mean active ghrelin levels and tended to increase mean leptin values (data not shown). *P < 0.05.
conflict with a second study that reported that skipping breakfast and skipping dinner both modestly increased energy expenditure, relative to eating three meals per day (30). However, the latter three-arm study was only partially randomized, and there was no difference in energy expenditure between skipping breakfast and skipping dinner, which suggests that the circadian timing of food intake does not significantly affect...
24-hour energy expenditure. Corroborating our null results for energy expenditure, a 5-week isocaloric controlled feeding study found that eTRF did not affect body weight when food intake was matched to the control arm (31). Together, this suggests that reduced food intake, which was detected in some (20,23,25,27) but not in other (18,21,22,24) studies relying on self-report, explains weight loss from eating earlier in the day.

Figure 8 Early time-restricted feeding (eTRF) (A) increased minimum hunger levels, (B) tended to decrease the mean desire to eat, (C) tended to increase mean fullness, (D) decreased minimum stomach fullness but tended to increase mean stomach fullness, (F) increased the maximum perceived body temperature (temp), and (G) decreased minimum energy levels. Daily means and ranges for all other facets of appetite and energy levels, including (E) capacity to eat and (H) awakeness, were similar. *P ≤ 0.05.
Although eTRF did not increase 24-hour energy expenditure in our study, it did increase TEF, estimated from data collected during the early postprandial period. This is consistent with data showing that TEF is higher in the morning than in the evening because of the circadian system (10-12). The increase in TEF in the eTRF arm was also likely due to the overlap in postprandial periods, which likely means that we overestimated TEF values during lunch and dinner in the eTRF arm. Nonetheless, extrapolating the observed increase in postprandial energy expenditure out to a 24-hour day (with some reasonable assumptions about the temporal profile of TEF) suggests that eTRF should have increased 24-hour energy expenditure by no more than approximately 20 to 40 kcal/d, which is roughly in line with the 10±16-kcal/d difference that we observed. Although we were not powered to detect differences in 24-hour energy expenditure as small as approximately 20 to 40 kcal/d, such small differences are considered clinically insignificant.

eTRF did affect substrate oxidation. eTRF increased 24-hour protein oxidation and decreased the 24-hour npRQ, particularly at nighttime. The increase in protein oxidation was likely due to enhanced gluconeogenesis associated with extended fasting. It will be important to determine whether eTRF negatively affects lean mass. Similarly, we suspect that the decrease in the 24-hour npRQ was indicative of enhanced fat oxidation and was likely due to the prolonged daily fasting period of eTRF rather than its circadian effects (38). Although two prior studies reported conflicting results on whether prolonged daily fasting (skipping breakfast or dinner) affected 24-hour fat oxidation (30,37), the studies were limited by the fact that they did not extend the fasting duration on the day prior to testing and therefore may have underestimated fat oxidation. By contrast, two longer-term studies, including one on time-restricted feeding, suggested that intermittent fasting may boost fat loss (39,40). However, such results are best viewed as suggestive, and more definitive trials are needed to test whether eTRF and other intermittent fasting interventions improve fat loss. It is also worth noting that we observed npRQ values below 0.71 at nighttime in some participants. Respiratory quotient values below 0.71 can arise when ketones are produced at higher rates than they are oxidized or when gluconeogenesis is accompanied by storage of glucose in muscles (41). However, because we did not measure ketone production or gluconeogenesis, whether this happened is speculative, and we cannot completely rule out other possibilities (41). Nonetheless, the overall temporal effects on substrate oxidation also improved metabolic flexibility, which may independently reduce the risk of obesity and type 2 diabetes (42).

We also investigated the effects of meal timing on metabolic hormones and appetite. We found that eTRF lowered mean values of the hunger hormone ghrelin (mostly in the morning) as well as increased levels of the satiety hormone PYY in the middle of the evening. Our data concur with a prior study that reported that 12 weeks of eating breakfast like a king and dinner like a pauper reduced the active ghrelin AUC throughout the waking day (18). eTRF also tended to decrease the mean desire to eat and increase fullness across the waking day. These improvements in appetite are corroborated by other meal-timing studies that have reported reductions in subjective appetite and/or food intake (18,20,25-27). It is also important to underscore that contrary to expectations, we found no evidence that daily intermittent fasting increased mean appetite levels, at least not when energy intake is matched to the control arm. Surprisingly and paradoxically, eTRF reduced swings in hunger (i.e., reduced the diurnal amplitude of hunger), making hunger levels more even-keeled throughout the day, which may reduce overeating or binge eating.

Despite the rigor of our study design, our trial had some limitations. First, our trial was powered to detect an 80-kcal/d difference in energy expenditure (Cohen’s d = 1.0); we cannot rule out that eTRF may more modestly increase energy expenditure by approximately 20 to 40 kcal/d. Second, we were able to draw blood only at two times of day rather than frequently during the 24-hour period, which limits the interpretation of our metabolic hormone data. Third, our intervention duration was short (only 4 days), which may not be long enough for metabolic and/or circadian adaptation to occur. Fourth, we did not fully characterize our participants’ habitual sleep and dietary habits at baseline. Lastly, our sample size was both relatively small and skewed toward men. Although we expect our results to be qualitatively generalizable, the effect sizes may be modulated by covariates such as biological sex because of known sex differences in substrate availability during fasting (43).

### Conclusion

The circadian timing of food intake does not appear to significantly affect 24-hour energy expenditure. Instead, our data suggest that meal-timing interventions facilitate weight loss primarily by suppressing appetite. Aligning food intake with circadian rhythms may therefore be a powerful strategy for reducing appetite and losing weight. The subset of meal-timing interventions that involve intermittent fasting, such as time-restricted feeding, may confer additional metabolic advantages by improving metabolic flexibility and increasing 24-hour fat oxidation. Further research is needed to determine the effects of meal timing on energy and fat metabolism.

### Acknowledgments

We deeply thank our study participants and the staff at PBRC. Study materials, including the study protocol and statistical analysis plan, can be obtained by emailing the corresponding author. Any sharing of deidentified study data will be governed by a data-transfer agreement.

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