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Intermittent Fasting as a Nutrition Approach against Obesity and Metabolic Disease

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Abstract

Purpose of review: Intermittent fasting (IF) has been proposed as a potential nutrition approach against obesity and metabolic disease. Although data from studies in rodents convincingly support the anti-obesity and cardiometabolic benefits of IF, its effects in human health are still debatable.

Recent findings: Recent studies have examined the effect of two IF approaches, i.e., alternate day fasting (ADF) and time-restricted eating (TRE), on weight loss and cardiometabolic risk factors. ADF seems to be an equally effective weight loss approach to caloric restriction, but adherence to ADF is more challenging. ADF improves cardiometabolic risk factors, while it may have superior metabolic benefits compared to caloric restriction in people with insulin resistance. TRE with *ad libitum* food intake is well-tolerated and induces 2–4% weight loss. Additionally, TRE may have metabolic benefits particularly in people with metabolically abnormal obesity even without weight loss.

Summary: IF is a promising nutritional approach against obesity and its related metabolic diseases. Further research is needed to: i) establish the long-term effectiveness of TRE in weight loss and metabolic health, ii) improve the long-term adherence to ADF and investigate its weight loss independent effects in metabolic health, and iii) determine the mechanisms underlying the potential cardiometabolic benefits of IF in humans.

Keywords

Time-restricted eating; alternate day fasting; glucose; insulin; lipids

INTRODUCTION

Obesity and its associated diseases constitute an important public health, financial, and social issue worldwide. Further, in the light of the recent novel coronavirus (SARS-CoV-2)

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pandemic, preliminary data suggest that obesity and its related metabolic complications are associated with adverse events from COVID-19 including death (14). Nutrition and physical activity are the first-line approaches for the prevention and treatment of obesity and its metabolic complications. However, their effectiveness is limited mostly due to the suboptimal long-term adherence. Intermittent fasting (IF) has attracted significant scientific and popular interest as a nutrition approach against obesity and its metabolic complications.

IF encompasses numerous distinct nutrition approaches that involve prolonged fasting including: i) *time-restricted eating (TRE)*, which involves the restriction of the daily eating period to 4–12 hours with no caloric intake for the rest of the day; ii) *alternate day fasting (ADF)*, which involves decreased or no caloric intake (~25 % of the daily energy needs usually as lunch or dinner) on the "fasting day" and *ad libitum* food intake during the "feast day"; iii) *periodic fasting* (also known as 5:2), which involves decreased caloric intake (~25% of the total energy needs usually as lunch) for two consecutive days and *ad libitum* caloric intake during the rest of the five days of the week; and iv) the *fasting mimicking diet* which involves consuming a low calorie (~30% of energy needs), high unsaturated fat diet for five days once a month or once every three or four months (6).

Results from studies in rodents support that IF improves body composition and systemic metabolic function (i.e., glucose homeostasis and atherosclerotic dyslipidemia) even without weight loss or caloric restriction (CR) (5). Apart from its systemic effects, IF also elicits tissue-specific metabolic adaptations including: i) adipose tissue remodeling (i.e., browning of white adipose tissue, increased brown adipose tissue thermogenesis, improved lipid metabolism, and decreased inflammation); ii) decreased liver fat content; iii) increased lean mass and endurance; iv) correction of the obesity-related perturbations in the diurnal rhythmicity (for TRE); v) increased autophagy in peripheral tissues; and vi) changes in gut microbiome (2, 10, 23). Although evidence from studies in rodents convincingly support the metabolic benefits of IF, its health effects in humans remain unclear and only a few studies have investigated this topic. The purpose of this manuscript is to summarize and critically evaluate the recent literature on the effect of IF on obesity and cardiometabolic health in humans. From 2018 onwards, the published IF-related trials have focused on TRE and ADF. Table 1 provides an overview of the studies discussed in this review.

IF, Weight Loss, Body Composition, and Energy Homeostasis

TRE.—TRE has shown promise as a weight management approach. The majority, but not all (1), recent studies support that 4–10-hr TRE with *ad libitum* caloric intake for 8–12 weeks induces 2.5–4% weight loss in people with excessive adiposity (3, 4, 7, 22). Current evidence support that the duration of the daily eating window (6 vs. 4 hours) does not affect the magnitude of the TRE-related weight loss (4). Although the reported TRE-induced weight loss did not reach the 5–7% threshold for "clinically meaningful" weight loss (i.e., weight loss that results to clinically significant improvements in cardiometabolic health), it is of great interest that participants managed to lose weight with *ad libitum* caloric intake. Similarly, the majority, but not all (7), recent studies supports that TRE decreases total body and/or visceral adiposity (1, 3, 4, 22). The effect of TRE on lean mass is currently unclear and some studies reported a TRE induced decrease in lean mass assessed by dual X-ray

absorptiometry (DXA) (3, 4). However, another TRE intervention, which also included high protein intake (1.6 g/kg) and resistance training, reported that TRE does not adversely affect lean mass accretion (assessed by using 4 compartment model by DXA and bioimpedance spectroscopy) in physically active young females (19).

To explore the potential mechanism(s) underlying the weight loss effects of TRE, some authors assessed participants' energy intake, physical activity, and energy expenditure during TRE. According to the results, TRE with *ad libitum* food and beverage consumption led to a spontaneous decrease in energy intake (8–27%) (1, 4, 7, 22) suggesting that CR may (at least partially) explain the TRE-induced weight loss. This hypothesis is further corroborated by the fact that adequate caloric intake during TRE can prevent weight loss (18). TRE may also decrease hunger and decrease satiety especially in the evening (16, 18). Only one study assessed the effect of TRE in energy homeostasis in healthy adults with obesity using whole-room indirect calorimetry (16). Six-hour TRE for four days did not affect 24-hr and resting energy expenditure (REE), but it increased diet-induced thermogenesis, protein and fat oxidation (16). The effect of TRE on energy expenditure needs to be studied in larger sample and after a longer TRE intervention. Changes in physical activity (assessed by using wearable activity monitors) do not seem to explain the TRE-induced weight loss (9, 11, 22).

ADF.—Consistent with earlier investigations (20), two recent studies further support that ADF leads to modest weight loss (9, 17). ADF for 4 weeks with no calorie intake during the "fasting" day and *ad libitum* food intake during the "feast" day leads to 4% weight loss and decreased body fat and lean mass (~2 kg) (17). These results suggest that participants do not fully compensate on the "feast" day for the fasting-induced caloric deficit of the previous day. Similarly, Gabel et al. reported that ADF resulted in 8% weight loss and 6 kg fat loss with no changes in lean mass and visceral adiposity after 12 months in people with obesity and insulin resistance (9). The observed body weight and fat loss was similar to the CR arm (9). These results are not surprising considering that adherence to ADF decreases with time and the participants tend to follow a dietary pattern that increasingly resembles CR. Differences in REE or physical activity do not appear to explain the ADF-induced weight loss (9, 17).

IF, glucose homeostasis, and insulin resistance

Insulin resistance and impaired glucose homeostasis are important milestones in the pathogenesis of type 2 diabetes. Recent studies investigated the effect of IF on indirect markers of glucose homeostasis (i.e., fasting plasma glucose) and insulin sensitivity (assessed by measuring plasma glucose and insulin during fasting or in response to an oral glucose tolerance test (OGTT)) (1, 3, 4, 7, 12, 22). Some studies also used continuous glucose monitoring to assess 24-hr glycemia (3, 11, 22) or a mixed meal tolerance test to assess postprandial glucose metabolism (11).

TRE.—The effect of TRE on glucose homeostasis and insulin resistance is debatable as recent studies have reported conflicting results. First, Antoni et al. reported a significant decrease in fasting plasma glucose after 10 weeks of TRE (1). Cienfuegos et al. reported that 4-hr and 6-hr TRE for 8 weeks equally improved fasting hyperinsulinemia and

the homeostatic model assessment of insulin resistance index (HOMA-IR) in people with obesity and insulin resistance, but without changes in fasting plasma glucose and glycosylated hemoglobin A1c (4). Conversely, a number of studies reported that 8–10-hr TRE with *ad libitum* caloric intake for ~12 weeks had no effect on glycemic control and fasting insulin concentration in people with excessive adiposity (3, 7, 22). However, for some of these studies, the authors reported trends for improved glycemia and fasting hyperinsulinemia (3, 22).

To investigate the effect of TRE and TRE timing on postprandial glucose metabolism, Hutchison performed a 7-day randomized cross-over trial to assess the effect of early TRE (8 am to 5 pm) and delayed TRE (12 pm to 9 pm) in men with excessive adiposity and high risk for type 2 diabetes (11). TRE (both early and delayed) decreased the incremental area under the curve (iAUC) for plasma glucose during a meal tolerance test. Although early TRE resulted to a greater decrease in the AUC for plasma glucose compared to delayed TRE, the difference was not statistically significant. Further research is needed to clarify the link between the timing of TRE and glucose homeostasis.

To avoid potential confounding due to change in weight status and dietary intake, two feeding studies assessed the effect of TRE in glucose homeostasis during weight maintenance. Six-hour TRE for 4 days improved 24-hr glycemia and decreased fasting plasma glucose and insulin in the morning, but not in the evening (12). Additionally, 6-hr TRE without weight loss for 5 weeks decreased plasma insulin concentration during fasting and OGTT without changes in plasma glucose levels suggesting that TRE may improve insulin sensitivity in people with prediabetes (18). The reasons underlying the discrepancies in the glycemic control related outcomes may be due to differences in duration and timing of TRE, fasting duration, the metabolic health status of the study participants, the indirect methods used for the assessment of glucose metabolism and insulin sensitivity, and small sample size.

ADF.—Two recent studies assessed the role of ADF on glucose metabolism and insulin resistance with mixed results (9, 17). Four weeks of ADF had no effect on indices of insulin sensitivity in healthy people without obesity (17). On the other hand, 12 months of ADF decreased fasting hyperinsulinemia with no change on plasma glucose suggesting that ADF may be more effective than CR for the treatment of insulin resistance (8). Differences in the metabolic health of the study participants and the duration of the study may explain the discrepancy in the reported outcomes between the two studies.

IF and plasma lipid and cholesterol metabolism

Elevated plasma triglycerides (TG) and cholesterol are important risk factors for the development of cardiovascular disease (15, 21). Accordingly, recent studies explored the effect of IF on lipemia.

TRE.—The effect of TRE on plasma TG and cholesterol concentration is currently unclear and recent studies have reported mixed and sometimes conflicting results.

- *TG.* The majority of studies support that 4–10-hr TRE with *ad libitum* food intake does not affect fasting plasma TG in people with excessive adiposity (1, 3, 4, 7, 22). Similarly, 6-hr TRE for four days had no effect on plasma TG (12). However, Hutchison et al. reported that 9-hr TRE for seven days led to a significant decrease on fasting plasma TG, but not the postprandial iAUC for TG (11). Conversely, five weeks of 6-hr TRE increased morning fasting plasma TG levels in people with pre-diabetes (18).
- *Total cholesterol.* Two recent studies support that about 10-hr TRE with *ad libitum* food intake decreases total cholesterol in people with metabolic syndrome (22) or marginally decreases total cholesterol in people with overweight (1). Two recent studies reported 4–8hr of TRE for 8–12 weeks had no effect on plasma total cholesterol concentration in people with obesity (4, 7). Conversely, two 6-hr TRE feeding studies reported an increase in plasma total cholesterol in the morning but not in the evening in people with overweight (12, 18).
- *Low density lipoprotein (LDL).* The majority of studies supports that TRE for 5–12 weeks has no effect on LDL cholesterol concentration in people with excessive adiposity (3, 4, 7, 18). Hence, 10-hr TRE for 12 weeks decreased LDL cholesterol and marginally decreased LDL particle size in people with metabolic syndrome (22). Similarly, Antoni et al. reported a trend for lower LDL cholesterol after 10 weeks of TRE in people with overweight (1). On the other hand, four days of 6-hr TRE increased fasting plasma LDL cholesterol in the morning but not in the evening in people with overweight (12).
- *High density lipoprotein (HDL).* The majority of the recent studies reported no change on plasma HDL cholesterol concentration with TRE (1, 3, 4, 7, 18), while two studies reported conflicting results. Four days of 6-hr TRE increased HDL cholesterol (12), while 10-hr TRE for 12 weeks decreased in HDL cholesterol in patients with metabolic syndrome (22).

The reasons for the conflicting results on the effect of TRE in lipemia are currently unclear. However, they may be related to differences in lipid kinetics with the duration of fasting (13) prior to the sample collection, timing of the TRE protocol, differences in the metabolic health of the participants, lack of functional assessments of lipid metabolism, or small sample size.

ADF.—Although previous studies have reported that ADF improves lipemia (20), the recent ADF trials reported no statistically significant effect on plasma total-, LDL-, or HDL-cholesterol and TG concentrations (9, 17). However, Stekovic et al. reported a significant improvement on the Framingham Risk Score (an index of 10-year risk for developing cardiovascular disease) after 4 weeks of TRE (17). This discrepancy may be attributable to lack of power as markers of lipemia were not the primary outcome of those studies.

IF and blood pressure

The effect of IF on blood pressure is currently debatable. The majority (4, 7, 18, 22), but not all (3), recent investigations support that TRE decreases systolic and/or diastolic blood pressure in people with overweight/obesity even without weight loss. In contrast, ADF had no effect on blood pressure (9, 17). Additionally, a few studies investigated the effect of IF on heart rate and pulse wave velocity (a clinical measure of arterial stiffness). ADF (4, 9, 17) and TRE (7, 18) had no effect on hearth rate. Finally, TRE for 5 weeks had no effect on pulse wave velocity in people with prediabetes (18), whereas ADF for a month decreased in pulse wave velocity in people without obesity (17) suggesting that ADF may improve arterial stiffness. Further research is needed to clarify the effect of IF in vascular health.

Safety and Adherence during IF

TRE is a safe nutrition intervention and appears to be tolerated well at least in the short-term. Recent TRE with daily eating window duration 8–10 hour studies reported low dropout rates (<10%) due to the intervention, but the dropout rate appears to increase to 20% with shorter eating window duration (1, 3, 4, 18, 22). Adherence to TRE is variable (about 65–90%), while TRE approaches with daily eating window greater than 8 hours achieve higher adherence rate (3, 4, 7, 22). Although none of the studies quantitatively assessed the long-term adherence to TRE, approximately 60% of participants were willing to continue TRE (1) or actually continued to follow TRE (even partially) beyond the study period (22). Nausea, diarrhea, headache, dizziness, constipation, and dry mouth are potential but infrequent adverse events of 4–8-h TRE (4, 8, 18). Except from dry mouth, the rest of adverse effects appear to subside after the first 3–4 weeks of TRE (4). Ten-hour TRE had no adverse effects (22) suggesting that the TRE interventions with longer daily eating period may be better tolerated. A gradual increase in the daily fasting period may further optimize adherence and minimize any potential adverse effects.

The recently published ADF studies do not provide extensive information about tolerance and adherence. However, data from previous studies support that ADF is associated with a higher dropout rate (~40%) compared to CR (~30%) suggesting that ADF may not be a feasible weight loss intervention for many individuals. Additionally, Gabel et al. reported that participants assigned to the ADF arm tended to eat a greater amount of calories than the prescribed energy intake during the “fasting” day and a lower amount of calories than the prescribed energy intake during the “feast day” further indicating that long term compliance to ADF is challenging (9). ADF with no calorie intake on the fasting day had no significant adverse effects in people without obesity (17).

SUMMARY

IF has attracted significant interest as a nutritional approach against obesity and its related metabolic complications. Recent studies reported new evidence on the effect of TRE and ADF on weight and cardiometabolic risk factors.

TRE is a promising nutrition intervention against obesity and its metabolic diseases. It is well-tolerated with no major adverse events. TRE with *ad libitum* food consumption may

lead to modest weight loss (2–4% in 3 months) and decreased adiposity likely due to decreased caloric intake. Preliminary data support that TRE may improve glucose and lipid metabolism and blood pressure particularly in people with metabolically abnormal obesity even without weight loss. Although the current literature provides valuable information on the potential metabolic benefits of TRE on cardiometabolic health, limitations in study design and experimental methods (i.e., indirect measures for the assessment of metabolic function, differences in fasting duration, testing limited primarily in the morning, the lack of an appropriate control group, lack of tissue-specific data or long-term data) limit the conclusions from those studies and contribute to discrepancies in reported study results.

ADF has been extensively investigated as an alternative nutrition approach against obesity and metabolic disease. ADF leads to clinically significant weight loss and decrease in adiposity similar to CR and improvements in glucose and lipid metabolism. However, adherence to ADF can be challenging. Preliminary data indicate that ADF may lead to superior improvements in insulin resistance compared to CR in people with obesity insulin resistance.

CONCLUSION

IF is an emerging nutritional approach for the prevention and treatment of obesity and its related metabolic diseases. Further research is needed to: i) establish the long-term effectiveness of TRE in weight loss, metabolic regulation, and quality of life, ii) improve the long-term adherence to ADF and investigate its weight loss independent effects in metabolic health, and iii) understand the mechanisms underlying the potential cardiometabolic benefits of IF in humans.

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ABBREVIATIONS

ADF	alternative day fasting
CR	caloric restriction
DXA	dual X-ray absorptiometry
HDL	high density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
iAUC	incremental area under the curve
LDL	low density lipoprotein
OGTT	oral glucose tolerance test
REE	resting energy expenditure

TG	triglycerides
TRE	time-restricted eating

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• of special interest

•• of outstanding interest

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KEY POINTS

- IF has recently attracted significant scientific and public interest as lifestyle approach against obesity and its related metabolic diseases.
- Recent data support that TRE with *ad libitum* food intake induces weight loss and it may improve cardiometabolic risk factors even without weight loss.
- ADF induces modest long-term weight loss and improvements in cardiometabolic risk factors, but long-term adherence to ADF can be particularly challenging.
- Further research is needed to determine the effect of IF in metabolic regulation in the whole-body and tissue-specific level.

Table 1.

Summary Table of Recent IF Studies

Author-Year & Study Design	Population	Treatment	Dietary intake and appetite	Body Wt Body comp.	Energy expenditure	Plasma Glucose and Insulin Sensitivity	Plasms/ Serum Lipid &Chol. Metab	Blood Pressure
Antoni et al. 2018 (1) 10-week trial	Adults with overweight (n=12F, 1M)	**TRE**: delayed breakfast and advanced dinner by 1.5 h each. Ad libitum EI **CON**: habitual lifestyle	**TRE vs. CON** ↓ EI	**TRE vs. CON** Ø body wt ↓ body fat NA lean mass	EE NA PA NA	**TRE vs. CON** ↓FBG Ø fasting insulin	**TRE vs. CON** Trend for ↓TCHOL & LDL-c Ø TG, HDL-c	NA
Chow et al. 2020 (3) 12-week RCT	Adults with overweight/ obesity & daily eating period ≥14h (n=17F, 3M)	**TRE:** 8-hr self-selected daily eating period. Ad libitum EI. **CON:** Ad libitum EI	**TRE vs. CON** ↓eating occasions NA EI	**TRE vs. CON** ↓ body wt & fat ↓ lean mass ↓ visceral fat ↓ leg lean mass Ø trunk or arm lean mass	**TRE vs. CON** Ø PA EE NA	**TRE vs. CON** Trend for ↑ time of glucose in range (70–180 mg/dl) Ø FBG, insulin, HbA1c, insulin sensitivity indices, 24-h mean glucose by CGM	**TRE vs. CON** Ø TG, HDL-c, LDL-c	**TRE vs. CON** Ø DBP/SBP
Cienfuegos et al. 2020 (4) 8-week RCT	Adults with obesity and insulin resistance (n=44F, 5M)	**4-hr TRE:** 1500–1900 daily eating period **6-hr TRE:** 1300–1900 daily eating period **CON:** habitual daily eating period Ad libitum EI	**TRE vs. CON** Ø diet composition ↓ EI (Ø 4-hr vs. 6-hr TRE)	**TRE vs. CON** ↓body wt ↓fat mass (Ø 4-hr vs. 6-hr TRE) ↓lean mass in 6-hr TRE (vs. 4-h TRE and CON) Ø visceral fat	Ø PA EE NA	**TRE vs. CON** Ø fasting glucose and % HbA1c ↓fasting insulin and HOMA-IR (Ø 4-hr vs. 6-hr TRE)	**TRE vs. CON** Ø HDL-c, LDL-c, TG	**TRE vs. CON** Trend for ↓DBP/SBP Ø heart rate
Gabel et al. 2018 (7) 12-week single-arm trial	Adults with obesity (n=20F 3M) vs. historical control (n=21F, 2M)	**TRE:** 8-hr daily eating period (1000–1800). Ad libitum EI. **CON:** keep usual daily eating habits for weight maintenance. Ad lib.	**TRE vs. CON** ↓ EI	**TRE vs. CON** ↓ body wt Ø fat, lean, and visceral fat mass	**TRE vs. CON** Ø PA Ø RMR	**TRE vs. CON** Ø FBG, insulin, HOMA-IR	**TRE vs. CON** Ø TCHOL, LDL-c, HDL-c, TG	**TRE vs. CON:** ↓ SBP Ø DBP, heart rate
Gabel et al. 2019 (9) 12-month RCT	Adults with obesity and insulin resistance (n=33F, 10M) Secondary data analysis of this study (20)	**CON:** Ad libitum EI. ***6-mo wt loss*** **ADF**: 25% kcal on fast day, 125% kcal on "feast" day **CR**: 75% kcal/d ***12-mo wt maintenance*** **ADF**: 50% kcal lunch	**ADF & CR vs. CON** 0–3 months feeding study Ø macronutrient, cholesterol, fiber intake **ADF & CR vs. prescribed EI:** ADF ↑ EI than prescribed on fast days/↓ EI	**ADF & CR vs. CON** ADF and CR ↓body wt and fat mass (No difference between ADF vs. CR) Ø lean mass, visceral fat	**ADF & CR vs. CON** Ø PA EE NA	**ADF & CR & CON** Ø FBG ↓ insulin ↓ HOMA-IR	**ADF & CR vs. CON** Ø TCHOL, LDL-c, HDL-c, TG	**ADF & CR vs. CON** Ø SBP/DBP Ø heart rate

Author-Year & Study Design	Population	Treatment	Dietary intake and appetite	Body Wt Body comp.	Energy expenditure	Plasma Glucose and Insulin Sensitivity	Plasms/ Serum Lipid &Chol. Metab	Blood Pressure
		only on fast day, 150% kcal on "feast" day **CR** (n=15): 100% kcal/d	than prescribed on "feast" days vs. CR ↓EI than prescribed					
Hutchison et al. 2019 (11) 7-day randomized cross-over trial	Adults with obesity and at risk for diabetes (n= 15M)	**CON:** ad libitum EI **TRE-e:** 9-hr daily eating period (0800–1700). Ad libitum EI. **TRE-d:** 9-hr daily eating period (1200–2100). Ad libitum EI.	**TRE vs. CON** Ø perceived hunger, fullness, desire to eat (Ø TRE-e vs. TRE-d) EI and diet composition: NA	**TRE vs. CON** Ø body wt Body composition NA.	**TRE vs. CON** Ø EE Ø PA	**TRE vs. CON** Mixed meal test: ↓ glucose iAUC (↓TRE-d vs. TRE-e) and trend for ↓ insulin iAUC Ø fasting insulin CGM : ↓ FBG with TRE-e, Ø 24-hr or fed glucose	**TRE vs. CON** Mixed meal test: ↓ fasting TG Ø TG iAUC Ø fasting FFA and FFA iAUC	NA
Jamshed et al. 2019 (12) Ravusssin et al. 2019 (16) 4-day randomized cross-over study	Adults with obesity (n= 4F, 7M)	**TRE**:6-hr daily eating period (0800–1400) **CON:** 12-hr daily eating period (0800–2000). Day 1–2: Ad libitum EI. Day 3–4: standardized eucaloric meals.	**TRE vs. CON** ↓ diurnal hunger amplitudes	**TRE vs CON** ↓ 0.2 kg body wt	**TRE vs. CON** Ø REE & 24h EE ↑ TEF ↓RQ	**TRE vs. CON** ↓ 24hr glycemia *Morning:* ↓ FBG, insulin, HOMA-IR, ↓3-h glucose after breakfast *Evening:* ↑insulin, HOMA-IR	**TRE vs. CON** *Morning:* ↑ LDL-c, HDL-c, TCHOL Ø TG *Evening:*Ø TCHOL, LDL-c, VLDL-c, HDL-c, TG	NA
Stekovic S et al. 2020 (17) 4-week RCT	Adults with BMI 22–30 (n=34F, 23M)	**ADF:** 0-kcal liquids only on fast days. Ad libitum EI on "feast" day. **Control:** Ad libitum EI.	**ADF vs. CON :** ↓ EI	**ADF vs. CON:** ↓ body wt ↓ fat mass ↓fat-to-lean ratio ↓lean mass	**ADF vs. CON:** Ø PA Ø REE on "feast" day	**ADF vs. CON :** Ø indices of insulin sensitivity Glucose NA	**ADF vs. CON:** Ø TCHOL, LDL-c, VLDL-c, HDL-c, TG	**ADF vs. CON:** ↓SBP, Ø DBP Ø heart rate ↓pulse wave velocity
Sutton et al. 2018 (18) 5-week randomized cross-over trial	Adults with overweight/ obesity and pre-diabetes (n=8M)	**TRE:** 6 h daily eating period. Dinner before 3 pm. Breakfast time 0630–0830. **CON:** 12-hr daily eating period	**TRE vs. CON:** Feeding trial ↓desire/ capacity to eat and ↑fullness in the evening	**TRE vs. CON :** Ø body wt NA body fat & lean mass	**TRE vs. CON:** PA NA EE NA	**TRE vs. CON:** Ø FBG or mean OGTT glucose ↓ fasting & mean OGTT insulin ↑ insulinogenic index	**TRE vs. CON: AM fasting** ↑ TG ↑ TCHOL Ø HDL-c, LDL-c	**TRE vs. CON: AM fasting** ↓ SBP/DBP Ø heart rate Ø pulse wave velocity
Wilkinson et al. 2019 (22) 12-week single-arm trial	Adults with obesity, metabolic syndrome & daily eating period ≥14h	**TRE:** 10-hr self-selected daily eating period. Ad libitum food intake.	**Post vs. Pre:** ↓ EI	**Post vs. Pre:** ↓ body wt & fat ↓ visceral fat	**Post vs. Pre:** Trend for ↓ daily activity counts EE NA	**Post vs. Pre:** Trend for ↓ in FBG, HbA1c, insulin Ø mean glucose by	**Post vs. Pre:** ↓ TCHOL ↓ LDL-c ↓ HDL-c Ø TG	**Post vs. Pre:** ↓ SBP/ DBP

Author-Year & Study Design	Population	Treatment	Dietary intake and appetite	Body Wt Body comp.	Energy expenditure	Plasma Glucose and Insulin Sensitivity	Plasms/ Serum Lipid &Chol. Metab	Blood Pressure
	(n= 6F,13M)					CGM and HOMA-IR		

ADF: alternate day fasting, CON: control CR: calorie restriction, DBP: diastolic blood pressure, EE: energy expenditure, EI: energy intake, FBG: fasting plasma glucose, FFA: free fatty acids, HDL-c: high density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment of insulin resistance, iAUC: incremental area under the curve, LDL-c: low density lipoprotein cholesterol, NA: no available data, OGTT: oral glucose tolerance test, PA: physical activity, REE: resting energy expenditure, RQ: respiratory quotient, SBP: systolic blood pressure, TCHOL: total cholesterol, TEF: thermal effect of food, TG: triglycerides, TRE: time-restricted eating, TRE-e: early TRE, TRE-d: delayed TRE, wt: weight, Ø: no effect, ↓: decreased, ↑: increased