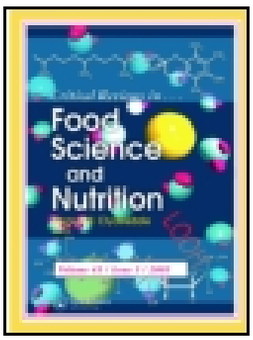

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Jéssica do Nascimento Queiroz , Rodrigo Cauduro Oliveira Macedo , Grant M. Tinsley & Alvaro Reischak-Oliveira (2020): Time-restricted eating and circadian rhythms: the biological clock is ticking, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1789550

To link to this article: https://doi.org/10.1080/10408398.2020.1789550

Published online: 14 Jul 2020.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1789550

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REVIEW

Time-restricted eating and circadian rhythms: the biological clock is ticking

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ABSTRACT

Meal timing may be a critical modulator of health outcomes due to complex interactions between circadian biology, nutrition and human metabolism. As such, approaches that aim to align food consumption with endogenous circadian rhythms are emerging in recent years. Time-restricted eating (TRE) consists of limiting daily nutrient consumption to a period of 4 to 12 hours in order to extend the time spent in the fasted state. TRE can induce positive effects on the health of individuals with overweight and obesity, including sustained weight loss, improvement in sleep patterns, reduction in blood pressure and oxidative stress markers and increased insulin sensitivity. However, it is not fully clear whether positive effects of TRE are due to reduced energy intake, body weight or the truncation of the daily eating window. In addition, null effects of TRE in some populations and on some parameters of cardiometabolic health have been documented. Some evidence indicates that greater promotion of health via TRE may be achieved if the nutrient intake period occurs earlier in the day. Despite some promise of this dietary strategy, the effects of performing TRE at different times of the day on human cardiometabolic health, as well as the safety and efficacy of this dietary approach in individuals with cardiometabolic impairments, need to be evaluated in additional controlled and long-term studies.

KEYWORDS

Circadian system; fasting; health; intermittent fasting; meal timing; time-restricted feeding

Highlights

- TRE improves clinical outcomes such as body weight, blood pressure and insulin sensitivity.
- TRE-induced benefits may be confounded by reduced energy intake and weight loss.
- TRE improves health outcomes through circadian-related mechanisms.
- Eating in alignment with circadian rhythms seems to improve cardiometabolic health.
- Limited evidence indicates TRE may be most beneficial when food intake is limited to earlier in the day.
- Human studies comparing TRE protocols at different times of the day are lacking;

Introduction

The prevalence of obesity has increased ~300% in the world population in the last several decades (González-Muniesa et al. 2017; Roberto et al. 2015), and according to World Health Organization reached 650 million individuals with obesity (World Health Organization 2020). Obesity, or excess weight in the form of fat mass, is related to increased non-communicable chronic diseases and mortality, decreased quality of life and life expectancy, and substantial economic burden (Blüher 2019; Williams et al. 2015). In order to control or reverse this pandemic and its well-documented adverse effects, several dietary approaches have been employed (Yannakoulia et al. 2019). In the last decade, intermittent fasting (IF) has emerged as an increasingly common alternative to traditional dietary strategies in both healthy and at-risk populations (Anton et al. 2018; Patterson and Sears 2017; Trepanowski et al. 2017).

Fasting is commonly defined as the total abstinence of energy-containing foods and beverages for periods ranging from 12 hours to 3 weeks, although some protocols employ modified fasting in which a minimal number of calories may be consumed. IF is a dietary strategy characterized by a voluntary period of eating privation, with absence of energy intake for true fasting or a drastic reduction for modified fasting,interle interspersed with regular periods of food and beverage intake (Longo and Mattson 2014). Although different classification groupings have been presented in the literature, non-religious IF protocols are commonly separated into modified fasting regimens (e.g., 5:2 diet), alternate-day fasting and time-restricted eating (TRE; humans), also known as time-restricted feeding (TRF; animals) (described in Table 1) (Patterson and Sears 2017; Wilkinson et al. 2020). The benefits of IF have been primarily observed in studies with animal models, in observational data on

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Table 1. Intermittent fasting (IF) types.

IF types	Definition
Modified fasting regimens	Protocols in which energy intake is drastically reduced on one or more days per week. On modified fasting days, it is common to allow the consumption of 20% to 25% of the daily energy requirements. The most used protocol is 5:2 diet, where there is food restriction on 2 days per week (consecutive or nonconsecutive), with *ad libitum* eating on the other 5 days. With complete fasting, these regimens have sometimes been termed whole-day fasting.
Alternate-day fasting (1:1)	Alternate fasting days (without food or energy-containing beverages) with eating *ad libitum* days. It is usually implemented as a 1:1 protocol, which consists of one day of food restriction followed by one day of feeding *ad libitum*. Modified alternate-day fasting, in which a small amount of energy intake is allowed on the "fasting" day, is commonly utilized.
Time-restricted eating	Daily food consumption restricted to a specified window, often 4 to 12 hours in duration, inducing extended fasting intervals. Generally, there are no dietary restrictions in the eating period.
Religious Ramadan Fasting	Food and water restriction from sunrise to sunset during the Ramadan month. Daily duration of fasting varies based on geography and corresponding time of year on Gregorian calendar. Commonly, a large meal is consumed after sunset and a smaller meal before dawn each day.

religious fasting (Ramadan) or in short-duration experimental studies with small samples. Included among these health effects are increased tissue repair, brain function and metabolic homeostasis, metabolic flexibility, mitochondrial biogenesis, as well as improvement in insulin sensitivity, reductions in fat mass, oxidative stress and blood pressure levels (de Cabo and Mattson 2019; Mattson et al. 2018; Teruya et al. 2019).

TRE, a form of IF, consists of limiting daily energy consumption to a period of 4 to 12 hours in order to extend the time spent in the fasted state (Francesco et al. 2018). Commonly, TRE programs aim to align the feeding-fasting cycle with circadian rhythms, thereby synchronizing the supply of food with the time period during which the body is best able to receive it (Chaix, Manoogian, et al. 2019). Previous studies in animal models, as well as in humans, indicate that TRE induces positive effects on cardiometabolic parameters, particularly when food consumption occurs in their respective active phases of the day (Chaix, Manoogian, et al. 2019; Gill and Panda 2015; Jamshed et al. 2019; Longo and Panda 2016; Sutton et al. 2018).

Much of modern society has almost uninterrupted access to food, especially products with high energy density and low nutritional quality, which can contribute to adverse health outcomes (Jiang and Turek 2018; Stenvers et al. 2019). In this way, nutritional strategies that seek to minimize unrestrained food consumption and its negative effects appear to be relevant to the modern food environment. Chrononutrition is an approach that aims to align food intake with endogenous circadian rhythms, based on observations that meal timing *per se* can influence health outcomes (Almoosawi et al. 2016; Aparecida Crispim and Carliana Mota 2019; Wehrens et al. 2017). Also, recent evidence indicates that TRE appears to be a promising dietary strategy to mitigate the chronodisruption and its known deleterious health effects (Chaix, Manoogian, et al. 2019). Thus, the purpose of the present review is to explore the current literature on the emerging nutritional strategies of chrononutrition and TRE. Also, we examine the major findings from studies that investigated the effects of TRE on cardiometabolic parameters of healthy persons and patients with overweight, obesity and metabolic disorders. Finally, a consideration of differential effects of TRE based on participant population and time of day is presented.

Circadian system

Research concerning the relationship between health and the circadian cycle has emerged in current years. The mammalian circadian system is composed of a central/master clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which controls several secondary clocks distributed in the brain (extra-SCN) and other organs, including liver, skeletal muscle, adipose tissue and pancreas (Rijo-Ferreira and Takahashi 2019; Roenneberg and Merrow 2016; Stenvers et al. 2019). Briefly, circadian clocks (central/master and peripheral/secondary) are intracellular mechanisms that generate self-sustained oscillations of approximately 24 hours by a set of proteins, called clock proteins, that work through autoregulatory feedback loops (Challet 2019; Rijo-Ferreira and Takahashi 2019).

The circadian cycle (from Latin *circa diem*, "about a day") can coordinate a series of biological, metabolic and behavioral processes that occur throughout the day in order to anticipate and adapt to the daily rhythmic changes (Roenneberg and Merrow 2016). The central and peripheral oscillators generate circadian rhythms that are self-sustaining and autonomous; however, external stimuli (*zeitgebers*) can change the circadian synchronization (Roenneberg and Merrow 2016). In the SCN, a central pacemaker is regulated mainly by the presence of light, through the retino-hypothalamic tract (Logan and McClung 2019; Stenvers et al. 2019) (Figure 1). While the master clock is controlled by the light-dark cycle, peripheral tissues are predominantly responsive to feeding (Arble et al. 2009). In particular, the composition of food (macronutrient content) and temporal pattern of food consumption seems to influence circadian oscillators of peripheral tissues, especially of the liver and adipose tissue (Arble et al. 2009; Logan and McClung 2019; Reinke and Asher 2019). The SCN also appears to have a role in eating behavior. Circadian control of food intake can be mediated by neuroanatomical connections that occur between the SCN and the arcuate nucleus, which is involved in the regulation of food intake (Mendoza et al. 2010). In addition to the central clock in the SCN also there are secondary brain clocks. A timing system influenced by food intake, known as a food clock, participates in the feeding-fasting cycle and controls food-anticipatory processes (Challet 2019). Communication between the master clock and the peripheral oscillators occurs through neural and hormonal signals (e.g., cortisol and melatonin), body

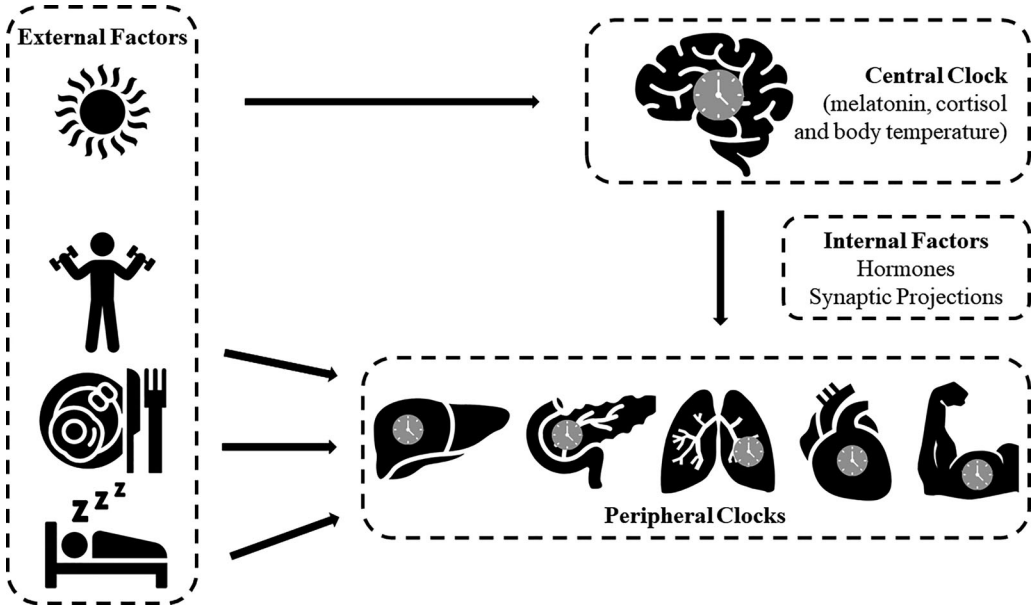

Figure 1. The circadian system is composed by a central clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and a series of peripheral clocks located in various organs of the body. Central clock is regulated mainly by light, while the peripheral clocks are regulated especially by the central clock and by external factors, such as the time and composition of meals, physical activity and sleep pattern.

temperature, autonomic nervous system (sympathetic and parasympathetic) and indirectly through the feeding-fasting, resting-activity and sleep-wake cycles (Jiang and Turek 2018; Stenvers et al. 2019). Together, the interaction between central clock, food clock and peripheral oscillators and the *zeitgebers* determine circadian rhythmicity (Roenneberg and Merrow 2016).

Evolutionarily, human beings became active during the day and inactive overnight. As such, an endogenous circadian system has developed to ensure that physiological processes are most active at propitious moments (Stenvers et al. 2019). However, modern society encourages behaviors that strongly contribute to chronodisruption and, consequently, the development of adverse health effects (Jiang and Turek 2018; Logan and McClung 2019; Scheer et al. 2009; Stenvers et al. 2019). Notable examples of these chronodisruptors include artificial lighting, social jetlag, shift work, eating jet lag (variability in the timing of food intake), as well as the nearly uninterrupted access to food, especially high energy density and low nutritional quality (Jiang and Turek 2018; Stenvers et al. 2019; Zerón-Rugerio et al. 2019).

When the external stimuli to which organisms are exposed are asynchronous with their endogenous circadian rhythms, the pathogenesis of metabolic diseases can be accentuated (Reinke and Asher 2019). Thus, improving the synchronization between external stimuli, such as the feeding-fasting cycle, with the endogenous rhythms of central and peripheral clocks may be an appropriate approach to minimize the prevalence and burden of cardiometabolic diseases (Stenvers et al. 2019).

Circadian control of feeding

Chrononutrition is an approach that aims to align food intake with endogenous circadian rhythms. In addition to food quality and quantity, meal timing may meaningfully influence health outcomes in humans and animals due to complex interactions between circadian biology, nutrition and human metabolism (Almoosawi et al. 2016; Asher and Sassone-Corsi 2015; Manoogian, Chaix, and Panda 2019). Although few studies have been conducted in humans, emerging data have indicated that the circadian system plays a crucial role in regulating lipid metabolism (Gooley 2016; Kessler et al. 2020), given that free fatty acids, low-density lipoprotein (LDL-c), total cholesterol (TC) and triglycerides (TG) present daytime variations that may exceed interindividual changes (van Kerkhof et al. 2015). A recent systematic review verified the differential effects of isocaloric meal consumption at different times of the day (day *vs.* night) on the postprandial lipemia responses (Bonham et al. 2019). When it was evaluated at night (20:00 – 4:00), higher TG plasma levels were observed, as well as a late peak in TG concentration, compared to postprandial lipemia analyzed during the day (7:00–16:00). These data suggest there is a nocturnal impairment in postprandial lipid metabolism, which may be a potential increasing mechanism of cardiovascular disease risk (Bonham et al. 2019). A recent cross-sectional study verified the relationship between the distribution of energy consumption throughout the day and the lipid profile of healthy Asian adults (Chen et al. 2019). It was observed that a higher energy intake at night (17:30–20:29), mainly due to fats, was associated with increased TC and LDL-c plasma levels. Additionally, the authors found that changing the intake of 100 kcal from night to morning or to noon was associated with decreased TC and LDL-c levels (Chen et al. 2019). Together, these data indicate there may be decrements in lipid metabolism at the end of the active biological phase/onset in humans.

In a previous review, Potter et al. (2016) pointed out that, in rats, restricting feeding to the end of the active phase or during the rest phase culminated in chronodisruptions and deleterious metabolic effects, possibly due to the

desynchronization of periods of high energy intake and the accompanying attenuation of energy expenditure (Potter et al. 2016). In humans, a similar situation is induced by religious fasting that occurs annually in the month of Ramadan. During this period, Muslims fast from energy and water consumption from sunrise to sunset, the duration of which varies based on geographical location and year, thereby limiting the eating period to the inactive phase (Trepanowski and Bloomer 2010). Nevertheless, previous studies have not consistently revealed adverse effects arising from the misalignment between the feeding phase and the active phase, induced by Ramadan fasting (Sadeghirad et al. 2014; Santos and Macedo 2018). In fact, some previous studies have reported modest and transient body weight loss and improvement in lipid profile during this period (Fernando et al. 2019; Sadeghirad et al. 2014; Santos and Macedo 2018; Trepanowski and Bloomer 2010). Considering that most studies that analyze Ramadan fasting are observational and present heterogeneous results (Sadeghirad et al. 2014; Trepanowski and Bloomer 2010), controlled studies should be performed to verify the discrepancy between findings in animal and human models that were fed on their respective inactive biological phases.

Several populations present high energy intake during the night (Almoosawi et al. 2016). In humans, glucose tolerance, peripheral sensitivity to insulin, β-pancreatic cells responsiveness, thermic effect of food and fatty acids oxidation in skeletal muscle appear to be higher in the morning than in the afternoon or at night, suggesting that human metabolism is optimized for food consumption in the earlier hours of the day (Morris et al. 2015; Poggiogalle, Jamshed, and Peterson 2018; Stenvers et al. 2019). In this sense, some studies have shown that feeding in alignment with endogenous circadian rhythms, i.e. allocating the period of highest energy intake to the first part of the day, culminated in positive effects on health (Garaulet et al. 2013; Gill and Panda 2015; Jakubowicz et al. 2013; Sutton et al. 2018). In an observational study, Garaulet et al. (2013) verified, in individuals with overweight and obesity undergoing a 20-week weight loss intervention, those who usually consumed lunch after 15:00 presented significantly higher insulin resistance, compared to those who performed this meal before 15:00 (Garaulet et al. 2013). Jakubowicz et al. (2013) examined the effects of a 12-week isocaloric diet, distributed differently throughout the day on the weight loss of women with obesity. Consuming approximately half of daily energy intake at breakfast proved to be more effective for weight loss and improvements in metabolic parameters as compared to the same energy intake at dinner (Jakubowicz et al. 2013). Furthermore, eating a higher proportion of calories at the beginning of the day and maintaining consistent periods of fasting at night were strategies proposed in recent research syntheses to mitigate cardiometabolic risk (St-Onge et al. 2017; Stenvers et al. 2019). A recent meta-analysis of cohort studies found that not consuming breakfast was associated with increased risk of type 2 diabetes mellitus (T2DM), especially when this occurs in 4 to 5 days per week (Ballon, Neuenschwander, and Schlesinger 2019). In contrast, another recent meta-analysis indicated that the omission of breakfast, compared to regular consumption of this meal, culminated in a lower daily energy intake and lower body weight in healthy adults (Sievert et al. 2019). However, this outcome seems to be related to lower daily energy intake rather than the absence of the beakfast meal *per se*.

In order to elucidate the meal frequency effects on metabolic parameters, a cross-over study compared the effects of consuming a single meal each day vs. isocaloric three meals a day in healthy individuals. During the one meal a day condition, participants extended their daily fasting period due to the requirement of consuming the single meal between 17:00 and 21:00 each day. At the end of 8 weeks, a significant elevation in fasting glycemia and increased glucose intolerance in the morning was observed in the single meal condition (Carlson et al. 2007). The cause of these negative outcomes may be explained by the high energy intake in a single meal or by the meal consumption at the end of the active phase, when glucose tolerance and insulin sensitivity are diminished compared to the earlier hours of the day (Morgan et al. 2003; Poggiogalle, Jamshed, and Peterson 2018). In addition to the glycemic effects, increased hunger perception, systolic and diastolic blood pressure, TC and LDL-c levels were observed in the single meal condition compared to 3 meals distributed throughout the day (Stote et al. 2007). Additionally, a slight reduction in fat mass and elevation of high-density lipoprotein cholesterol (HDL-c) were observed in the one meal per day condition. It is important to highlight that the aforementioned studies evaluted the effects of different meal frequencies but did not evaluate the effects of altering the timing of energy intake within a given meal frequency (Carlson et al. 2007; Stote et al. 2007). Overall, these results suggest that a higher energy intake at the end of the day may not be beneficial to health, despite the increased duration of the daily fasting period. However, this investigation required consumption of sufficient energy to promote weight maintenance, and some participants reported extreme fullness and difficulty finishing the required allotment of food in the one meal per day condition (Stote et al. 2007). As such, the implementation of such a strategy in a free-living setting may exert differential effects due to the likliehood of energy restriction when individuals are free to adjust energy intake according to their preferences. Nonetheless, the aforementioned controlled trials indicate that reducing the duration of the eating window without attendant energy restriction may be insufficient to improve cardiometabolic parameters when feeding is not aligned with biological circadian rhythms. Much of the current interest in TRE as a dietary strategy relates to the aim of aligning the timing of food intake to the usual active phase of animals and humans in order to reduce circadian desynchronization and, consequently, the development of cardiometabolic complication risks.

Time-restricted eating/feeding

A regular and robust daily cycle of feeding and fasting that limits the energy intake to a specific day period and allows

adequate time spent in the fasted state may contribute to improvements in metabolic parameters and behavioral patterns, as well as attenuating harmful effects of chronodisruption (Adamovich et al. 2014; Chaix et al. 2014; Challet 2019; Manoogian, Chaix, and Panda 2019; Sutton et al. 2018). Based on this perspective, TRE emerged as a dietary strategy that consists of limiting the eating period to 4 to 12 hours, thus prolonging the duration of daily fasting. In general, energy intake is not controlled *per se,* although the truncation of the eating/feeding period may result in energy restriction (Francesco et al. 2018). Previous studies with rodents and *Drosophila* found positive effects of TRF, including reductions in levels of TC and fasting glycemia, decreased body weight, fat mass, dysbiosis and inflammation, increased energy expenditure and motor control, in addition to improvement of sleep patterns and cardiac function (Chaix, Manoogian, et al. 2019; Longo and Panda 2016).

In this way, previous studies have shown nocturnal rodents exposed to a high-fat diet during their inactive (diurnal) phase had significantly higher weight gain compared to those who were fed the same diet in the usual active phase (Arble et al. 2009; Hatori et al. 2012). A recent study found that mice fed an *ad libitum* high-fat diet increased weight and developed metabolic disorders, such as hepatic steatosis, dyslipidemia and glucose intolerance. In contrast, mice that consumed a high-fat diet for a determined period (9-10 hours during the active phase) did not present such complications (Chaix, Lin, et al. 2019). These data show that, in animal models, TRF during the active biological phase, compared to *ad libitum* intake, may result in body weight loss and beneficial moduclation of metabolic and clinical parameters. In addition, this may occur independently of energy balance changes and in the context of high-fat and fructose diets are offered (Chaix et al. 2014; Chaix, Lin, et al. 2019; Hatori et al. 2012; Smith et al. 2019), which are potentially obesogenic and harmful to health (Lu et al. 2018; Stanhope 2012). Thus, restricting feeding to a specific period of the day may be a promising dietary strategy. However, as mentioned, these results are mainly derived from animal studies, and it would be premature to assume that the same physiological consequences would occur in humans.

Human studies with TRE interventions have recently emerged and indicate that this form of IF seems to improve cardiometabolic health (Pellegrini et al. 2020; Waldman, Renteria, and Mcallister 2020). We identified, through an extensive search on electronic databases, eighteen trials in humans that investigated the TRE-induced effects on cardiometabolic outcomes, especially lipid and glycemic parameters, and body weight (Anton et al. 2019; Antoni et al. 2018; Gabel et al. 2018; Gill and Panda 2015; Hutchison et al. 2019; Jamshed et al. 2019; Kesztyüs et al. 2019; LeCheminant et al. 2013; Martens et al. 2020; McAllister et al. 2020; Moro et al. 2016; Parr et al. 2020; Ravussin et al. 2019; Sutton et al. 2018; Tinsley et al. 2017; Tinsley et al. 2019; Wilkinson et al. 2020; Zeb et al. 2020). Eligibility criteria included human studies, written in English, Portuguese or Spanish and without restriction on the date of publication. References of the retrieved papers were also screened. Gill and Panda (2015) observed that about 50% of the 156 participants in their investigation followed an eating period exceeding 15 hours per day. The authors selected a sub-sample of eight overweight participants and truncated the period of daily energy intake to a self-selected window of 10–12 hours. After 16 weeks of TRE, subjects improved sleep pattern, reduced body weight by 4% and maintained this weight loss after a one-year follow-up. However, with the TRE protocol application, there was a reduction of ∼20% total energy intake, especially due to the reduced consumption of alcoholic beverages and late-night snacks (Gill and Panda 2015). In a pilot study, Antoni et al. (2018) investigated the effects of 10 weeks of TRE on weight, body composition, and biochemical markers in adults with overweight. Participants in the TRE group were instructed to delay and advance the first and last meal of the day, respectively, by 1.5 hours each, while the control group followed their usual diet without restrictions. The TRE group reduced the total daily feeding window by about 4.5 hours, causing an unintentional decrease in energy intake of approximately 680 kcal/day. Compared to the control group, TRE significantly reduced fasting glycemia and fat mass, but there was no difference between groups in body weight, TG, TC, HDL-c, LDL-c, and insulin concentrations (Antoni et al. 2018). Similarly, other studies have observed an unintentional reduction in energy intake concurrent with a truncated eating window induced by TRE (Gabel et al. 2018; LeCheminant et al. 2013; Wilkinson et al. 2020). These data suggest that TRE without caloric reduction, as implemented in some animal investigations, may be less achievable in humans due to spontaneous energy restriction. Thus, it is still unclear whether the beneficial effects of TRE observed in humans are derived from energy restriction, weight loss or the delimitation of an eating period *per se*. Regardless, the finding that TRE may be a simple strategy to promote a reduction in energy intake may indicate its utility as a behavioral strategy to promote weight loss and its attendant health benefits.

Sutton et al. (2018) investigated a subtype of TRE, called early TRE (eTRE), in which feeding occurs early in the day to be optimally aligned with endogenous circadian rhythms. The authors demonstrated that eTRE with a 6-hour eating period (8:00 – 14:00), applied for 5 weeks, provided independent benefits of energy restriction and weight loss in eight middle-aged men with obesity and prediabetes. In the eTRE condition, participants showed improvement in insulin sensitivity, greater β-pancreatic cells responsiveness, as well as important reductions in blood pressure levels, in oxidative stress markers and in hunger perception at night, compared to the control condition (eating period of 12 hours; 8:00 – 20:00). However, fasting plasma TG levels were significantly higher after eTRE condition, and fasting plasma TC levels were significantly reduced after the control condition (Sutton et al. 2018). In a recent randomized crossover trial, men with overweight/obesity completed 5 days in two conditions separated by a 10-day washout

period between trials. Similar to Sutton et al. (2018), a harmful response in lipid metabolism was observed after TRE condition (8-hour feeding period; 10:00-18:00) compared to an extended feeding window (15-hour feeding period; 7:00-22:00) (Parr et al. 2020). Similar results were found in a randomized crossover trial, in which adults with overweight completed 4 days in two conditions separated by a 3.5-5-week washout period. Completing a 6-hour eating window (8:00–14:00), eTRE condition reduced fasting glucose, homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin in the morning, but increased fasting insulin and HOMA-IR in the evening, relative to the control condition (8:00 – 20:00). Even though the intervention was only 4 days, eTRE decreased 24-hour mean glucose levels and glycemic excursions and increased fasting levels of TC, LDL-c, HDL-c and β-hydroxybutyrate in the morning, compared to control condition (Jamshed et al. 2019). In contrast to previous studies (Jamshed et al. 2019; Parr et al. 2020; Sutton et al. 2018), a recent study found an improvement in the lipid profile (levels of TG, TC and HDL-c) of healthy men after 25 days of TRE with nocturnal feeding (8-hour feeding period; 19:30 – 3:30), compared to non-TRE (Zeb et al. 2020). Collectively, these data indicate that limiting the eating period to the early moments of the day (eTRE) in order to better align eating with circadian rhythms may promote select beneficial health outcomes, especially on glucose metabolism. However, the findings of possible deleterious effects on blood lipids warrants further investigation. Additionally, these studies compared the effects of eTRE to an extended feeding window spanning from the beginning to the end of the day. Few studies have investigated the effects of TRE applied at different times within the active phase. These investigations, which are likely to occur in the near future, will be informative due to the previously described circadian fluctuations in physiological processes related to energy metabolism and other cellular functions (Challet 2019; Poggiogalle, Jamshed, and Peterson 2018; Stenvers et al. 2019).

A recent randomized crossover trial evaluated the effects of eTRE compared to delayed TRE, on glucose tolerance in men with obesity and at risk for T2DM (Hutchison et al. 2019). Both TRE conditions were implemented for one week and were separated by a 2-week washout period. In contrast to the studies above, the daily eating period was 9 hours in the two protocols (eTRE: 8:00 – 17:00; delayed TRE: 12:00 – 21:00). TRE, regardless of timing, improved glucose tolerance in response to a test meal and decreased fasting triglycerides. Although mean fasting glucose assessed via continuous glucose monitor improved over time in the eTRE group only, the values did not significantly differ between conditions. Additionally, there was no significant difference between protocols in most other outcomes, including no effect of either TRE schedule on insulin, fatty acid concentrations, and gastrointestinal hormones. Thus, it seems that the TRE improves glycemic response to a 3-hour mixed-nutrient meal test, in men at risk for T2DM, regardless of when the TRE eating window occurs within the day (Hutchison et al. 2019).

The aforementioned studies were performed in adults without metabolic disorders. Recently, Wilkinson et al. (2020) analyzed, in a single-arm study, the TRE effects in people with obesity and metabolic syndrome. After a 12-week TRE program with a self-selected 10-hour feeding window, participants reduced body weight, fat mass, LDL-c, TC, and systolic and diastolic blood pressure. There were no improvements in the levels of glucose, insulin, glycated hemoglobin, TG, HDL-c, mean glucose, as well in sleep quality. Similar to previous studies, TRE caused a reduction in the caloric intake of the subjects despite no recommendations to change the diet beyond the eating window (Wilkinson et al. 2020). Another pilot study found that, after 3 months of TRE, modest but significant reductions in body weight, body mass index, waist circumference, waist-to-height ratio, and levels of glycated hemoglobin in primary care patients with abdominal obesity (Kesztyüs et al. 2019). However, as in several other studies, positive effects of TRE on the lipid profile were not observed. Due to the absence of a control group in both studies (Kesztyüs et al. 2019; Wilkinson et al. 2020), further investigations are needed to elucidate the effects of TRE in populations with cardiometabolic diseases. As stated, most clinical studies focused on young and middle-aged adults with overweight and obesity, so the benefits and the absence of adverse effects that were observed in these studies may not be generalized (Gabel, Hoddy, and Varady 2019; Kesztyüs et al. 2019; Sutton et al. 2018; Wilkinson et al. 2020). In aging populations at risk for loss of muscle strength and function, it has been questioned whether the potential benefits of TRE outweight potential risks of missed eating opportunities, particularly given the importance of dietary-protein-induced stimulation of muscle protein synthesis (Tinsley and Paoli 2019).

Anton et al. (2019) in a pilot study, reported weight loss after 4 weeks of TRE in older people with overweight, but body composition was not evaluated. This study demonstrated neither negative nor positive effects of TRE on physical function, cognitive function, quality of life, anthropometric and metabolic parameters in this population (Anton et al. 2019). Additionally, adverse effects were minor and infrequent, and high feasibility of TRE was observed in this investigation (Lee et al. 2020). In a recent randomized controlled crossover pilot study, null effects were observed in most of the cardiometabolic parameters after 6 weeks of TRE compared to normal eating in healthy middle-aged and older adults under free-living conditions (Martens et al. 2020). However, similar to some other studies (Jamshed et al. 2019; Parr et al. 2020; Sutton et al. 2018), a moderate increase in TC and LDL-c levels following the TRE condition compared with normal feeding condition was observed. Nevertheless, TRE demonstrated to be a feasible and well-tolerated dietary strategy. Still, losses of body weight, muscle mass and bone mineral density were not reported in the studied population. More studies are needed to elucidate the impact of TRE on health of the elderly populations because this type of IF can reduce the daily opportunities to consume calories and proteins and, consequently, aggravate age-related muscle loss (Tinsley and Paoli 2019). Thus, the lack

of clear positive results in the aforementioned studies (Anton et al. 2019; Martens et al. 2020), as well as possible unwanted effects of TRE, for now, do not seem to support the benefits of this dietary strategy in the older people as compared to current eating paradigms.

A small number of studies have evaluated the effects of TRE in combination with exercise training on health parameters and adaptations to exercise (Moro et al. 2016; Tinsley et al. 2017, 2019). After an 8-week strength training program, trained men undergoing TRE (8-hour eating period; 12:00 – 20:00) presented a significant reduction in fat mass and TG levels compared to the 12-hour feeding group (8:00 – 20:00). Also, TRE significantly reduced anabolic hormone concentrations but not fat-free mass (Moro et al. 2016). Similarly, Tinsley et al. (2019) reported no impairment of fat-free mass gains, skeletal muscle hypertrophy and maximal strength in active females performing 8 weeks of TRE (12:00 – 20:00) plus progressive resistance training, compared to a control group with an eating window of approximately 13 hours (Tinsley et al. 2019). Tinsley et al. (2017) also examined the effects of 8 weeks of resistance training in young physically active men. In contrast to the other investigations, TRE was performed only on days without strength exercise and the eating period was 4 hours/day. Compared to the group with unrestricted time to eat, no significant differences were found in weight and body composition parameters, although a possible attenuation of lean soft tissue gain due to reduced protein intake in the TRE group was suggested (Tinsley et al. 2017). These data indicate that with adequate energy and protein intake, TRE may not harm strength training benefits. Thus, TRE in association with resistance training seems to neither result in definitive improvements in health outcomes nor compromise adaptations to exercise training in young and healthy people. Studies examining the effects of TRE in association with aerobic training were not found to date. Table 2 provides summary information from studies investigating the TRE effects on cardiometabolic parameters and related outcomes in humans. In this table, we have not included studies that investigated religious fasting due to the common occurrence of confouding factors in these studies.

Final considerations and perspectives

Altogether, previous studies provide promising data concerning the benefits of TRE on human health. However, duration of interventions (4 days to 16 weeks), timing of eating period within a day, length of eating period (4 to 10 hours) and fasting duration (14 to 20 hours) are divergent among studies. Moreover, it is important to highlight that the investigated populations also varied meaningfully between studies. Investigations reporting null effects after TRE were usually performed in young and active or trained subjects, and this may explain the absence of clear benefits as compared to existing dietary paradigms (McAllister et al. 2020; Moro et al. 2016; Tinsley et al. 2017, 2019). Although many studies have been conducted with metabolically healthy populations, the presence of overweight and obesity may contribute to the more evident emergence of positive responses to TRE protocols (Gabel et al. 2018; Gill and Panda 2015; Hutchison et al. 2019; Sutton et al. 2018). A limited number of investigations aimed at aligning eating periods with circadian rhythms through eTRE have reported promising results on cardiometabolic and body composition parameters in populations with overweight or obesity (Antoni et al. 2018; Hutchison et al. 2019; Jamshed et al. 2019; Ravussin et al. 2019; Sutton et al. 2018). Positive but modest results were also observed in TRE investigations in which daily eating terminated in the evening (~19:00) in healthy young people and those with obesity, with and without metabolic impairment (Gabel et al. 2018; LeCheminant et al. 2013; Moro et al. 2016; Parr et al. 2020; Tinsley et al. 2019; Wilkinson et al. 2020). Together, these findings may suggest that the physiologically ideal time for food consumption could be in the earlier hours of the day, in order to promote alignment of the feeding-fasting cycle with the endogenous circadian rhythms of human metabolism and, consequently, to induce positive results in cardiometabolic health, especially of individuals with overweight and obesity. However, some data have indicated circadian rhythms in hunger, with the daily peak in the biological evening (~20:00) (Scheer, Morris, and Shea 2013) which may indicate that eTRE could be more difficult behaviorally for some individuals. Nonetheless, it also seems that an individual's chronotype may be important to consider in order to achieve greater adherence and enhance long-term health benefits (Munoz et al. 2019). At present, the very limited number of direct comparisons of eTRE to TRE with a later eating window preclude definitive conclusions. Ultimately, additional investigation is needed to further define the long-term impact of various TRE protocols on the health and disease risk of different populations.

Conclusion

In summary, advances in chrononutrition reveal that, aside from what and how much to eat, when to eat may also be critical for health. Human studies investigating the effects of TRE on cardiometabolic health are recently emerging. In this review, we observed divergent results of TRE interventions. This may be due to the fact that the relatively small number of existing studies have been conducted with different populations, with uncontrolled and short-term designs, and with different durations and times of the day for the eating window. Despite this, TRE may be a promising approach to promote weight loss and improvements in cardiometabolic health of persons with overweight and obesity. While this may be especially true when the eating window is placed near the beginning of the day with the fasting period at the end of the active biological phase, additional research is needed to confirm this. Therefore, the effects of performing TRE at different times of the day on human cardiometabolic health, as well as the safety, effectiveness and viability of this dietary approach in individuals with cardiometabolic impairments and older people need to be evaluated in controlled and long-term studies.

Table 2. Studies of time-restricted eating interventions in humans.

Study	Type of Study	Participants (n)	Duration (weeks)	Feeding/ Fasting Time (hours)	Eating Period	Diet	Training/ Physical Activity Control	Outcomes Pre vs. post TRE	Outcomes TRE vs. Control
(Antoni et al. 2018)	Pilot Study. Non-Randomized Clinical Trial	13 adults with overweight 1) TRE: 7 (6 W and 1 M) 2) GC: 6 W	10	8/16	1) TRE: Reduction of 3 h of feeding compared to usual: postpone in 1,5 h the first meal and advance in 1,5 h the last meal 2) CG: No time restriction	No dietary prescription	No physical activity control and/or physical training prescription	BW: ↔ % Fat: ↓ Fasting glucose: ↔ Fasting insulin: ↔ TG: ↔ LDL-c: ↔ HDL-c: ↔ TC: ↔	BW: ↔ % Fat: ↓ Fasting glucose: ↓ Fasting insulin: ↔ TG: ↔ LDL-c: ↔ HDL-c: ↔ TC: ↔
(Anton et al. 2019)	One Group, Pilot Study (Pre-Post Design)	10 sedentary older adults with overweight (≥ 65 years; 6 W and 4 M)	4	8/16	Self-selected 8-hour feeding window	No dietary prescription	No physical activity control and/or physical training prescription	BW: ↓ Blood glucose: ↔ Waist Circumference: ↔	NA
(Gabel et al. 2018)	Historically Controlled Pilot Study.	46 adults with obesity 1) TRE: 23 (20 W and 3 M) 2) HCG: 23 (21 W and 2 M)	12	8/16	1) TRE: 10:00-18:00 2) HCG: No time restriction	Self- reported dietary intake (no dietary prescription): 1) TRE: 1335 Kcal/day 46 CHO (%) 37 LIP (%) 17 PTN (%) 2) HCG: 1654 Kcal/day 45 CHO (%) 38 LIP (%) 17 PTN (%)	Steps count measured with a pedometer. TRE: 7443 steps/days HCG: 6967 steps/day	BW: ↔ FM: ↓ FFM: ↔ TC: ↔ LDL-c: ↔ HDL-c: ↔ TG: ↓ Fasting glycemia: ↔ Fasting insulin: ↓ HOMA-IR: ↓	BW: ↓ FM: ↔ FFM: ↔ TC: ↔ LDL-c: ↔ HDL-c: ↔ TG: ↔ Fasting glycemia: ↔ Fasting insulin: ↔ HOMA-IR: ↔
(Gill and Panda 2015)	One Group, Pilot Study	8 adults with overweight and obesity (5 M and 3 W)	16	10/14	Self-selected 10-hour feeding window	No dietary prescription	No physical activity control and/or training prescription	BW: ↓ Subjective hunger sensation at night: ↓	NA
(Hutchison et al. 2019)	Crossover Randomized Clinical Trial	15 men with obesity	7-day	9/15	1) eTRE: 8:00-17:00. 2) dTRE: 12:00-21:00	No dietary prescription	Energy expenditure, number of steps, and time spent sleeping - measured by the SenseWear armband. There was no effect of treatment on total energy expenditure, the number of steps, or duration of sleep.	eTRE: BW: ↓ Fasting glucose: ↔ Fasting insulin: ↔ Glucose iAUC: ↓ Mean fasting glucose by CGM: ↔ Mean fed blood glucose by CGM: ↓ Fasting TG: ↓ TG iAUC: ↔ dTRE: BW: ↓ Fasting glucose: ↔ Fasting insulin: ↔ Glucose iAUC: ↓ Mean fasting glucose by CGM: ↔ Mean fed blood glucose by CGM: ↔ Fasting TG: ↓ TG iAUC: ↔	eTRE vs dTRE: BW: ↔ Fasting glucose: ↔ Fasting insulin: ↔ glucose iAUC: ↔ Mean fasting glucose by CGM: ↔ Mean fed blood glucose by CGM: ↔ Mean 24-hour blood glucose concentration: ↔ Fasting TG: ↔ TG iAUC: ↔
(Jamshed et al. 2019)	Crossover Randomized Controlled Trial	11 adults with overweight (7 M and 4 W)	4-day	6/18	1) eTRE: 8:00-14:00 2) CC: 8:00-20:00	Dietary Prescription (eTRE and CC): 50% CHO 35% LIP 15% PTN 3 meals/day: Each meal (33% of the daily energy requirements)	No physical activity control and/or training prescription	NA	Mean 24-hour glucose levels and glycemic excursions: ↓
(Kesztyüs et al. 2019)	One Group, Pilot Study (pre–post design)	40 Adults with components of the metabolic syndrome. (31W and 9 M)	12	8-9/ 15-16	Self-selected 8/9-hour feeding window	No dietary prescription	No physical activity control and/or training prescription	BW: ↓ Waist Circumference: ↓ Waist-to-height ratio: ↓ HbA1c: ↓ HDL-c: ↔ LDL-c: ↔ TG: ↔ TC: ↔	NA

(LeCheminant et al. 2013)	Crossover Non-Randomized Trial	27 young men with normal weight	2	13/11	1) TRE: 6:00-19:00 2) CC: No time restriction	Self- reported dietary intake (no dietary prescription): 1) TRE: 2420 Kcal/day 49 CHO (%) 35 LIP (%) 16 PTN (%) 2) CC: 2664 Kcal/ day 48 CHO (%) 37 LIP (%) 15 PTN (%)	No physical activity control and/or physical training prescription	BW: TRE: −0,4kg CC: + 0,6kg	BW: ↓ Subjective feeling of hunger in the morning: ↑
(Martens et al. 2020)	Crossover Randomized Controlled Trial.	22 healthy midlife and older adults.	6	8/16	TRE: Self-selected 8-hour feeding window. CC: No time restriction	No dietary prescription.	Physical activity was estimated using the Community Healthy Activities Model Program for Seniors (CHAMPS).	NA	BW: ↔ BMD: ↔ Leg FM: ↑ FFM: ↔ TC: ↑ LDL-c: ↑ Subjective feeling of hunger: ↓ AUC insulin and glucose: ↔ IL-6: ↔
(McAllister et al. 2020)	Non-blinded, Randomized Pre-Post Pilot Study	22 physically active men TRE *ad libitum:* 12 TRE isocaloric: 10	4	8/16	Self-selected 8-hour feeding window	TRE *ad libitum:* instructed to eat as many calories as desired for satiation. TRE isocaloric: instructed observe their daily caloric intake and stay within 300 Kcal of habitual dietary intake.	No physical activity control and/or training prescription	TRE *ad libitum* and TRE isocaloric: BW: ↓ %Fat: ↓ FM: ↓ Glucose: ↔ HDL-c: ↑ LDL-c: ↔ TC:HDL-c ratio: ↔ TG: ↔ CT: ↔ Adiponectin: ↑ Cortisol: ↔ Insulin: ↔ Subjective feeling of hunger: ↔	TRE *ad libitum* vs. TRE isocaloric: BW: ↑ %Fat: ↑ FM: ↑ FFM: ↑ Glucose: ↔ HDL-c: ↔ TG: ↔ CT: ↑ LDL-c: ↑ TC:HDL-c ratio: ↑ Cortisol: ↑ Insulin: ↑ Adiponectin: ↓ Subjective feeling of hunger: ↔
(Moro et al. 2016)	Single-blind, Randomized Clinical Trial	34 strength trained men 1) TRE: 17 2) CG: 17	8	8/16	1) TRE: 12:00-20:00 2) CG: 8:00-20:00	Self- reported dietary intake (no dietary prescription). 1) TRE: 2735 Kcal/day 51 CHO (%) 25 LIP (%) 23 PTN (%) 2) CG: 2910 Kcal/ day 55 CHO (%) 22 LIP (%) 22 PTN (%)	ST 3x/week 85-90% 1RM 3 sets 6 to 8 repetitions Exercise session between 16:00 and 18:00	FFM: ↔ FM: ↓ RER: ↓ Glucose: ↓ Insulin: ↓ TG: ↓ HDL-c: ↑ LDL-c: ↔ CT: ↔ Leptin: ↓ Adiponectin: ↑ IL-6: ↓ TNF-α: ↓ IL-1β: ↓	FFM: ↔ FM: ↓ RER: ↔ Glucose: ↔ Insulin: ↔ TG: ↓ HDL-c: ↔ LDL-c: ↔ CT: ↔ Leptin: ↓ Adiponectin: ↑ IL-6: ↔ TNF-α: ↔ IL-1β: ↓
(Parr et al. 2020)	Crossover Randomized Controlled Trial.	11 sedentary men with overweight/ obesity	5-day	8/16	1) TRE: 10:00-18:00 2) CC: 7:00-22:00	Dietary Prescription (TRE and CC): 50% LIP 30% CHO 20% PTN	Physical activity levels by inclinometer (tri-axial physical activity monitor adhered to the thigh) and by an accelerometer worn over the right hip and fastened around the waist.	NA	Peak Glucose (venous and intestitial): ↔ Peak Insulin: ↔ Peak NEFA: ↑ Peak TG: ↑ AUC24h NEFA: ↑ AUC24h C-Peptide: ↓ AUC24h Glucose (venous and intestitial), Insulin, TG, Cortisol, PYY, Leptin, GLP-1 and GIP: ↔

(*continued*)

Table 2. Continued.

Study	Type of Study	Participants (n)	Duration (weeks)	Feeding/ Fasting Time (hours)	Eating Period	Diet	Training/ Physical Activity Control	Outcomes Pre vs. post TRE	Outcomes TRE vs. Control
(Ravussin et al. 2019)	Crossover Randomized Controlled Trial	11 adults with overweight (7 M and 4 W)	4-day	6/18	1) eTRE: 8:00-14:00 2) CC: 8:00-20:00	Dietary Prescription (eTRE and CC): 50% CHO 35% LIP 15% PTN 3 meals/day: Each meal (33% of the daily energy requirements)	No physical activity control and/or training prescription	NA	24-hour EE: ↔ TEF: ↑ Ghrelin: ↓ Metabolic Flexibility: ↑ RER: ↓ Protein oxidation: ↑ Fat oxidation: ↑
(Sutton et al. 2018)	Non-blinded, Crossover Randomized Controlled Trial	8 men with obesity and prediabetes.	5	6/18	1) eTRE: 8:00-14:00 2) CC: 8:00-20:00	Dietary Prescription (eTRE and CC): 50% CHO 35% LIP 15% PTN 3 meals/day: Each meal (33% of the daily energy requirements)	No physical activity control and/or training prescription	β-cells responsiveness: ↑ Fasting glycemia: ↔ Mean glucose: ↔ Fasting insulin: ↓ Mean insulin: ↓ Insulin resistance: ↓ TG: ↑ CT: ↔ HDL-c: ↔ LDL-c: ↔ IL-6: ↔	β-cells responsiveness: ↑ Fasting glycemia: ↔ Mean glucose: ↔ Fasting insulin: ↓ Mean insulin: ↓ Insulin resistance: ↓ TG: ↑ CT: ↑ HDL-c: ↔ LDL-c: ↔ IL-6: ↔
(Tinsley et al. 2017)	Randomized Controlled Trial	18 young men, healthy and physically active 1) TRE + ST: 10 2) ND + ST: 8	8	4/20	1) TRE + ST: ST days (3d): No time restriction Days without ST (4d): 4 h window between 16:00 and 24:00 2) ND + ST: No time restriction	Self- reported dietary intake (no dietary prescription): 1) TRE + ST: 13,144 Kcal/ week 46 CHO (%) 36 LIP (%) 19 PTN (%) 2) ND + ST: 14,746 Kcal/ week 48 CHO (%) 35 LIP (%) 18 PTN (%)	ST 3x/week 8-12 RM 4 sets per exercise interval between ser of 90 seconds	BW: ↔ FFM: ↔ FM: ↔ % Fat: ↔	BW: ↔ FFM: ↔ FM: ↔ % Fat: ↔
(Tinsley et al. 2019)	Randomized Controlled Trial	17 Young and active women 1) TRE + ST: 8 2) CG + ST: 9	8	8/16	1) TRE + ST: 12:00-20:00 2) GC + ST: 8:00-20:00	Self- reported dietary intake (no dietary prescription): 1) TRE + ST: 1624 Kcal/ day 39 CHO (%) 34 LIP (%) 27 PTN (%) 2) CG + ST: 1570 Kcal 42 CHO (%) 32 LIP (%) 27 PTN (%)	Physical activity levels by accelerometer. Progressive Resistance Training 3 nonconsecutive days each week 2 different upper- and lower-body sessions alternated 6-12 RM 4 to 5 sets per exercise Exercise session between 12:00 and 18:00	RER: ↔ FM: ↓ FFM: ↑ % Fat: ↓ Glucose: ↔ Insulin: ↔ Cholesterol: ↔ VLDL-c: ↔ HDL-c: ↔ TG: ↔ LDL-c: ↔	RER: ↔ FM: ↓ FFM: ↔ % Fat: ↔ Glucose: ↔ Insulin: ↔ Cholesterol: ↔ VLDL-c: ↔ HDL-c: ↔ TG: ↔ LDL-c: ↔
(Wilkinson et al. 2020)	One group, non-blinded, pilot study (pre-post design)	19 Middle-aged individuals with metabolic syndrome. (6W and 13 M)	12	10/14	Self-selected 10-hour feeding window	No dietary prescription	There were no significant changes in activity (measured by actigraphy).	BW: ↓ % Fat: ↓ Waist circumference: ↓ Blood glucose (CGM): ↔ Fasting glucose: ↔ Fasting Insulin: ↔ HOMA-IR: ↔ HbA1c (%): ↔ TC: ↓ LDL-c: ↓ HDL-c: ↔ TG: ↔	NA
(Zeb et al. 2020)	Randomized Clinical Trial	Healthy young men. 1) TRE: 56 2) non-TRE: 24	25-day	8/16	1) TRE: 19:30-3:30 2) Non-TRE: No time restriction	No dietary prescription	No physical activity control and/or training prescription	TC: ↓ LDL-c: ↔ HDL-c: ↔ TG: ↓	TC: ↓ LDL-c: ↔ HDL-c: ↑ TG: ↓

BMD: Bone Mineral Density; BW: Body Weight; CC: Control Condition; CG: Control Group; CHO: Carbohydrates; CGM: continuous glucose monitor; dTRE: Delayed-Time-restricted eating; EE: Energy Expenditure; eTRE: Early-Time-restricted eating; FFM: Fat-Free Mass; FM: Fat Mass; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide 1; HbA1c: hemoglobin A1c; HCG: Historical Control Group; HDL-c: High-Density Lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; iAUC: incremental area under the curve; IL-6: Interleukin-6; LDL-c: Low-Density Lipoprotein; LIP: Lipids; NA: Not Applicable; ND: Normal Diet; PTN: Proteins; PYY: Peptide Tyrosine Tyrosine; RER: Respiratory Exchange Ratio; RM: Repetition Maximum; ST: Strength Training; TC: Total Cholesterol; TEF: Thermic Effect of Food; TRE: Time-restricted eating; VLDL-c: very low-density lipoprotein cholesterol;. ↑: Increased Levels; ↓: Decreased Levels ↔: No difference.

Declaration of interest

GMT serves as a consultant to and received consulting payments from a company (Burn LLC) that may be affected by the research reported in the enclosed paper. As a consultant, GMT provided research-based information on intermittent fasting for the development of a commercial smartphone application targeted to those who practice intermittent fasting. JNQ, RCOM and ARO declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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