

## Review

## Time-Restricted Eating: Benefits, Mechanisms, and Challenges in Translation

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**Eating out of phase with daily circadian rhythms induces metabolic desynchrony in peripheral metabolic organs and may increase chronic disease risk. Time-restricted eating (TRE) is a dietary approach that consolidates all calorie intake to 6- to 10-h periods during the active phase of the day, without necessarily altering diet quality and quantity. TRE reduces body weight, improves glucose tolerance, protects from hepatosteatosis, increases metabolic flexibility, reduces atherogenic lipids and blood pressure, and improves gut function and cardiometabolic health in preclinical studies. This review discusses the importance of meal timing on the circadian system, the metabolic health benefits of TRE in preclinical models and humans, the possible mechanisms of action, the challenges we face in implementing TRE in humans, and the possible consequences of delaying initiation of TRE.**

## INTRODUCTION

Lifestyle-induced metabolic diseases, such as type 2 diabetes (T2D) and cardiovascular disease, are often associated with obesity, reductions in physical activity and increased consumption of energy-dense foods. Accumulating evidence suggests that *when* we eat may be another contributing factor to chronic disease progression (Andrzejczak et al., 2011). Lengthened daily eating patterns, in excess of 14 h/day, were evident in studies conducted in the USA and India, with less than 25% of caloric intake occurring prior to 1 pm (Gill and Panda, 2015; Gupta et al., 2017). Time-restricted eating (TRE, also known as time-restricted feeding, TRF) is a novel dietary tool that recommends individuals shorten the duration of the daily eating window, without altering calorie intake or diet quality. TRE restores circadian rhythms and imparts pleiotropic metabolic benefits in animal models (Chaix et al., 2014; Delahaye et al., 2018; Gill et al., 2015; Hatori et al., 2012; Olsen et al., 2017; Villanueva et al., 2019; Wang et al., 2018; Woodie et al., 2018). TRE also reduces body weight and fat mass, improves glucose tolerance and reduces blood pressure in humans, particularly in those with overweight or obesity (Figure 1) (Gabel et al., 2018; Gill and Panda, 2015; Hutchison et al., 2019; Sutton et al., 2018; Wilkinson et al., 2019). The studies to date in humans are limited in size and duration, and the effectiveness and acceptability of TRE in the general population remains unclear. The majority of TRE studies have also initiated the eating window early in the active phase, presumably to maximize the metabolic benefits. This review will discuss the metabolic benefits of TRE in preclinical models and the possible mechanisms of action. We also discuss the likely challenges of implementing TRE in humans and the possible consequences of delaying initiation of TRE.

## REGULATION OF CENTRAL AND PERIPHERAL CLOCK MACHINERY

Circadian rhythms are ubiquitous periodic oscillations in internal biological process that direct behavior and metabolism such as hormonal signaling, body temperature, nutrient absorption, and metabolism (Dongen 2017; Espelund et al., 2005; Panda et al., 2002; Reppert and Weaver, 2002). At the molecular level, circadian rhythms arise from tightly controlled autonomous interlocked genetic transcriptional feedback loop that involves *circadian locomotor output cycles kaput* (*clock*) and *brain and muscle ARNT like protein 1* (*bmal1*) as positive transcriptional factors for *period* (*per1*, *per2*, *per3*) and *cryptochrome* (*cry1*, *cry2*) genes (extensively reviewed in Hastings et al., 2018). The translation products of *per* and *cry* dimerize and act as negative regulators by inhibiting *clock* and *bmal1*. An additional feedback loop involves the transcriptional regulation of *bmal1* by *retinoic acid related orphan receptor* (*rorα*) and *nuclear receptor subfamily 1, group D, member 1* (*rev-erbα*). One cycle of this feedback loop takes ~24 h and is the basis of circadian rhythms in many organisms. The suprachiasmatic nucleus (SCN) is considered the master regulator of circadian rhythms and is primarily entrained by the light-dark cycle. This feedback loop also operates in

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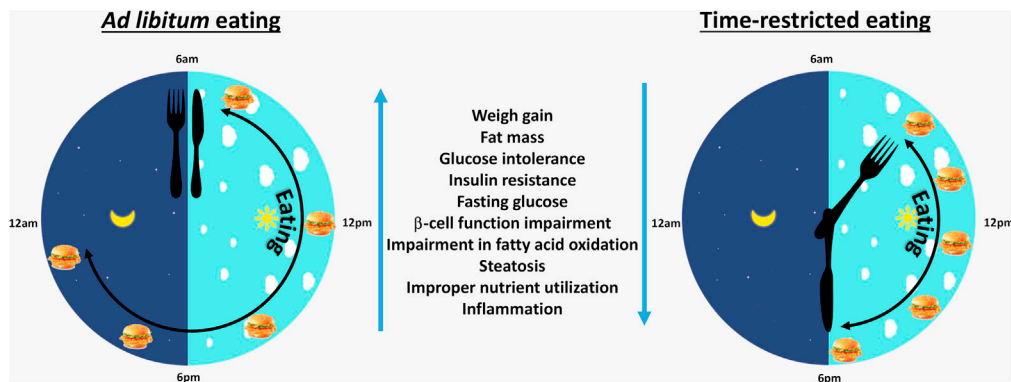
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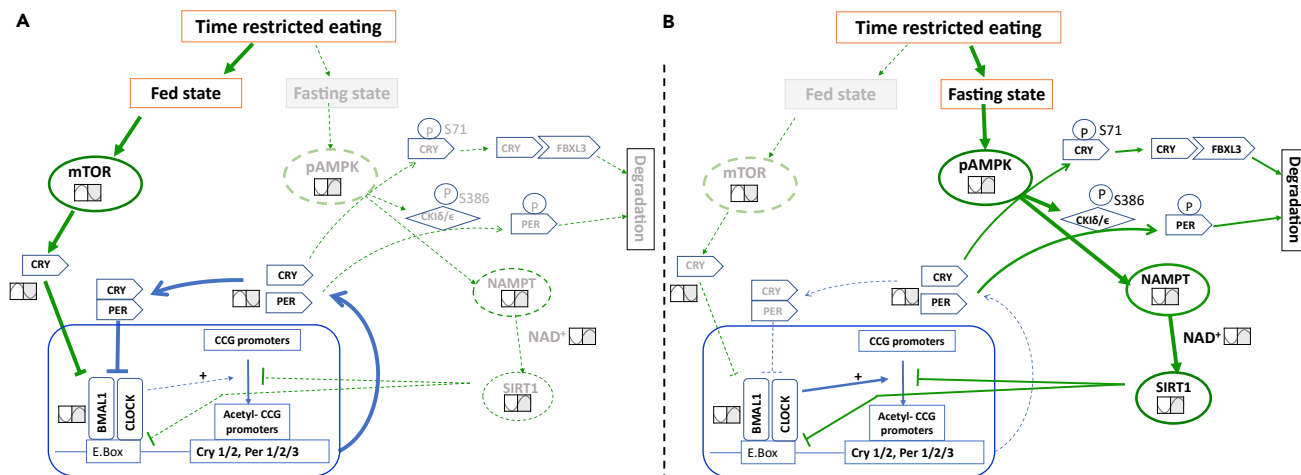
**Figure 1. TRE Metabolic Benefits**

peripheral tissues, including the liver, skeletal muscle, adipose tissue, pancreas, and intestine, which are not directly entrained by light (Reppert and Weaver, 2002; Yoo et al., 2004).

Peripheral clocks are exquisitely sensitive to the fasting-feeding cycle and, as discussed in the next section, can be uncoupled from the central clock through modifications in meal delivery (Damiola et al., 2000). At the molecular level, fasting increases the AMP/ATP ratio, activating 5' AMP-activated protein kinase (AMPK). This in turn phosphorylates serine71 of *cry1*, reducing its stability (Lamia et al., 2009). AMPK also regulates the activity of Casein kinase I epsilon via its phosphorylation at serine389, which is a critical regulator of *per* phosphorylation and stability (Meng et al., 2008). Nicotinamide adenine dinucleotide (NAD<sup>+</sup>) is a cofactor of several key pathophysiological enzymes and an absolute requirement of sirtuin 1 (SIRT1, a NAD<sup>+</sup>-dependent histone deacetylase). The majority of cellular NAD<sup>+</sup> comes from its salvage pathway where nicotinamide phosphoribosyltransferase (NAMPT) is the rate-limiting enzyme (Poljsak, 2018; Zhang et al., 2017). Fasting activates NAMPT, thus increasing the cellular availability of NAD<sup>+</sup>, activating SIRT1. Activated SIRT1 has been shown to directly bind with *clock:bmal1* and repress the transcription of *per2* (Ramsey et al., 2009). Thus, fasting also reduces both transcription and stability of *per* and *cry*, which de-represses *clock:bmal1* targets and increases their amplitude (Lamia et al., 2009; Um et al., 2007). SIRT1 has also been described to regulate the acetyltransferase activity of *clock* (Doi et al., 2006; Nakahata et al., 2008). In contrast, the mechanistic target of rapamycin (mTOR), a nutrient-activated serine/threonine protein kinase, is activated during the fed state. This post-transcriptionally induces *cry1* through an unknown mechanism (Ramanathan et al., 2018). Feeding also suppressed NAMPT function, reduced cellular NAD<sup>+</sup>, inactivating SIRT1. This abrogated SIRT1-mediated suppression of *clock:bmal1* and increased *per2* transcription (Ramsey et al., 2009). Hence, fasting increases the positive limb of circadian clock (*clock* and *bmal1*), whereas feeding increases the negative limb of circadian clock (*cry* and *per*).

### MEALTIME IS A STRONG ENTRAINING CUE OF PERIPHERAL CLOCKS AND SUBSEQUENTLY IMPACTS METABOLISM AND RISK FACTORS FOR CHRONIC DISEASE

Disrupted feeding therefore has a marked effect on the expression of the molecular clock in peripheral tissues (Jiang and Turek, 2017) and uncouples this from the SCN (Damiola et al., 2000). For example, restricting food access solely to the light phase in mice, when this nocturnal animal normally sleeps, completely reversed the phase of the circadian clock in liver, stomach, intestine, heart, pancreas, and kidney, without affecting the phase in the SCN (Damiola et al., 2000; Davidson et al., 2003). Simply delaying meals by 4 h also resulted in a phase shift in the circadian clock in mouse liver of a similar length (Shimizu et al., 2018). Delaying a single breakfast meal by 5 h also delayed expression of genes under *per* control in human adipose tissue (Wehrens et al., 2017). Conversely, studies have shown that rhythmic feeding was sufficient to maintain circadian rhythms of clock genes in peripheral tissues during constant light or darkness or following lesion of SCN (Hamaguchi et al., 2015; Kolbe et al., 2019; Novakova et al., 2011). These findings show that cues from the fasting-feeding cycle are more powerful entraining cues for peripheral clocks than the light-dark cycle (Figure 2) (Damiola et al., 2000; Wang et al., 2017).



**Figure 2. TRE Regulation of Peripheral Circadian Clocks**

TRE can reprogram circadian clock in the fasting state via AMPK and in the fed state via mTOR.

(A) In the fed state, nutrient availability activates mTOR. Activated mTOR induces Cry, which represses *Clock:Bmal1*.

(B) In the fasting state, nutrient depletion activates AMPK that directly and indirectly enhances phosphorylation on cry, and per. Phosphorylation is key for degradation of these proteins. Next, AMPK can activate SIRT1 activity via NAMPT. SIRT1 binds with clock:bmal1 and represses the transcription of *per2*. The acetyltransferase activity of *clock* is counteracted by SIRT1. Blue arrows represent core clock machinery, green arrows represent effect of TRE. AMPK, AMP-activated protein kinase; bmal1, brain and muscle arnt like 1; CCG, clock-controlled genes; CK, casein kinase; clock, circadian locomotor output cycle kaput; cry, cryptochrome; mTOR, mechanistic target of rapamycin; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyl transferase; per, period; SIRT1, sirtuin1.

Disrupting molecular clocks by altering feeding behaviors has subsequent impacts on metabolism in animal models. Reversing the phase of clock genes in peripheral organs by daytime restricted feeding was associated with weight gain, dyslipidemia, and fatty liver as compared with animals that were paired to an equivalent calorie level solely during the active phase (Bray et al., 2013; Yasumoto et al., 2016). This also reversed the phase of several genes involved in glucose homeostasis such as *glut2*, *pyruvate kinase*, *glucokinase*, and *glycogen synthase* in liver and several genes involved in lipid homeostasis such as *acetyl CoA carboxylase*, *diacylglycerol-O-acyltransferase*, *medium chain acylCoA dehydrogenase* in liver, muscle, and epididymal fat (Bray et al., 2013; Yasumoto et al., 2016). Daytime restricted feeding also reversed the phase of insulin, leptin, and ghrelin in plasma compared with mice fed only during nighttime (Yasumoto et al., 2016).

Similarly, a rotating light cycle (a mimic of shift work) altered the phase and reduced oscillation of clock genes in liver and caused higher weight gain, increased hepatosteatosis, and reduced  $\beta$  cell function and glucose-stimulated insulin secretion (Christie et al., 2018; Gale et al., 2011; Zhong et al., 2019). Chow fed mice under rotating light cycle also had altered phase of insulin and corticosterone in plasma and transcription factors *FOXO1*, *PPAR $\alpha$* , and *PPAR $\gamma$*  in liver (Zhong et al., 2019), whereas, high-fat diet (HFD)-fed mice under rotating light cycle completely lost the rhythmic expression of lipogenic gene *acyl-CoA carboxylase* in liver (Christie et al., 2018).

Furthermore, delaying the feeding phase by just 4 h shifted peripheral clocks and increased weight gain in rats exposed to HFD (Shimizu et al., 2018). Meal delay also delayed the peak of several genes involved in glucose homeostasis, such as *glucokinase*, *glucose 6 phosphatase*, and *phosphoenol pyruvate carboxykinase*, and several genes and transcription factors involved in lipid homeostasis, such as *SREBP*, *PPAR $\alpha$* , *fatty acid synthase*, *carnitine palmitoyl transferase*, and *malic enzyme* in liver. Likewise, meal delay also delayed the peak time of insulin, free fatty acids, and bile acids in plasma and circadian rise in body temperature (Shimizu et al., 2018).

## HEALTH EFFECTS OF TRE IN ANIMAL MODELS AND HUMANS

### TRE Induces Pleiotropic Metabolic Health Benefits in Animal Models of Obesity and Aging

TRE, defined here as the provision of food for up to 12 h during the active phase, is commonly known as TRF in animal studies to depict the eating window or food availability is externally controlled. TRE limited

weight and fat gain and protected nocturnal mice and diurnal flies from the metabolic consequences of HFD (Chaix et al., 2014; Delahaye et al., 2018; Gill et al., 2015; Hatori et al., 2012; Olsen et al., 2017; Sundaram and Yan, 2016; Villanueva et al., 2019; Woodie et al., 2018). This included protection from inflammation (Sherman et al., 2011) and immune responses (Cisse et al., 2018) and enhanced bile acid synthesis facilitating cholesterol excretion (Chaix et al., 2014) and reduced cholesterol levels (Delahaye et al., 2018). TRE also prevented age- and HFD-induced reductions in cardiac contractile function (Gill et al., 2015; Tsai et al., 2013) in mice and flies and restored HFD-induced loss of gastric vagal afferent mechanosensitivity (Kentish et al., 2018). TRE restored HFD-induced dampening of the circadian rhythms in the gut microbiome (Hu et al., 2019; Zarrinpar et al., 2014) and circadian rhythms in fatty acid oxidation (Chaix et al., 2019; Hatori et al., 2012). Thus, TRE has pleiotropic metabolic benefits to protect against chronic disease in mice and flies and importantly was able to reverse the consequences of obesity (Chaix et al., 2014) and aging (Duncan et al., 2016). The beneficial effects were also evident when TRE was implemented 5 days per week and food access was allowed *ad libitum* during weekends (Chaix et al., 2014; Olsen et al., 2017) in HFD-fed mice.

At the molecular level, TRE increased the amplitude of expression of AMPK and mTOR (Hatori et al., 2012; Sherman et al., 2012) (Figure 2) and *NAMPT* in the liver of mice that were fed HFD (Chaix et al., 2019). TRE also increased the amplitude of ribosomal protein phospho-S6 in skeletal muscle during the active phase (Chaix et al., 2014), suggesting increased mTOR activation during feeding. TRE increased the amplitude of *cry1* and *per1* in the liver of mice fed chow (Greenwell et al., 2019) and restored the amplitude of *bmal1*, *cry1*, *per2*, and *rev-erba* in mice that were fed HFD (Hatori et al., 2012). In liver, TRE reduced the amplitude of *pyruvate carboxylase* and *glucose 6-phosphatase*, and increased *glucokinase* during the active phase (Chaix et al., 2014; Hatori et al., 2012), potentially underpinning reductions in hepatic glucose production and increased glucose utilization. TRE also reduced the amplitude of genes *fatty acid synthase*, *stearoyl CoA desaturase*, and *fatty acid elongase* during the active phase and increased the amplitude of *hepatic triglyceride lipase* during the inactive phase, which was associated with reduced lipid storage and increased triglyceride hydrolysis.

Importantly, Chaix et al. examined the effects of TRE in mice that were deficient in *cry1* and *cry2* at the whole-body level or deficient in *bmal1* and *reverb $\alpha$*  &  $\beta$  only in liver. In this study, TRE was effective to restore robust rhythms in genes involved in energy metabolism and nutrient utilization in the liver from all knockouts, as well as nutrient signaling pathways with higher AMPK and mTOR function (higher pS6 levels during feeding) in fasting and fed states, respectively. TRE also protected knockouts from HFD-induced weight gain, glucose intolerance, hepatic steatosis, and dyslipidemia (Chaix et al., 2019). This study proves that sustaining daily rhythms in the fasting and feeding cycle is sufficient to maintain metabolic homeostasis, independently of circadian clocks (Chaix et al., 2019).

From studies to date, it is difficult to separate whether TRE improves health, independently of changes in calorie intake. Certainly, some studies have suggested this (Chaix et al. 2014, 2019; Hatori et al., 2012). However, food intake is difficult to measure accurately, and other studies have shown lower calorie consumption in TRE mice that are fed a HFD (Delahaye et al., 2018; Sundaram and Yan, 2016) and marked weight loss initially in response to TRE (Kentish et al., 2018; Sundaram and Yan, 2016). Thus, some of the metabolic benefits of TRE may well be mediated by calorie restriction and weight loss. However, a recent study in mice showed that TRE improved glucose tolerance and reduced HOMA-IR in rats following high fat-high sugar diet, without any weight loss (Woodie et al., 2018). A recent human study also supported the notion that TRE imparts metabolic benefits independently of changes in body weight (Sutton et al., 2018).

### TRE Improves Metabolic Health Outcomes in Humans

Several TRE protocols with daily meal intakes prescribed from 4 to 13 h have been trialed in people of normal weight and overweight (summarized in Table 1), although all of these trials are short-term (4 days to 16 weeks) and conducted in a small number of participants. The majority of studies report modest reductions in body weight and fat mass (Anton et al., 2019; Chow et al., 2020; Gabel et al., 2018; Gill and Panda, 2015; LeCheminant et al., 2013; Moro et al., 2016; Stote et al., 2007; Wilkinson et al., 2019) and waist circumference (Kesztyus et al., 2019). TRE also reduced plasma triglycerides and inflammatory markers (LeCheminant et al., 2013; Moro et al., 2016), blood pressure, and atherogenic lipids (Gabel et al., 2020; Wilkinson et al., 2019). Some studies have also reported significant improvement in glucose control

Study	Participants	Trial length	Design	Intervention, Meal Time	Major Findings
(Carlson et al., 2007; Stote et al., 2007)	n = 15 (10 females, 5 males), normal weight	8 weeks	Cross-over	TRE: one isocaloric meal (5 pm–9 pm) Control: three meals/day	↓ Body weight, fat mass, blood pressure, glucose tolerance ↑ Fasting glucose
(LeCheminant et al., 2013)	n = 27 males, normal weight	2 weeks	Cross-over	TRE: 13-h TRE (6 am–7 pm) Control: AL	↓ 0.4 kg Body weight (vs ↑ 0.6 kg control condition)
(Gill and Panda, 2015)	n = 8 (3 females, 5 males), overweight	16 weeks	Within participant	TRE: 10–11 h (self-selected) Baseline: >14 h	↓ Body weight
(Moro et al., 2016)	n = 34 males, normal weight	8 weeks	Randomized controlled	TRE: 8 h (1 pm–8 pm) Control: 12 h (8 am–8 pm)	↓ Fat mass, fasting glucose, fasting insulin, total testosterone, IGF-1
(Tinsley et al., 2017)	n = 18 resistance trained males (10: RT-TRE; 8: RT-AL)	8 weeks	Randomized controlled	TRE: 4 h (anytime 4 pm to midnight) for 4 days a week Control: AL	↔ Body weight, fat mass
(Gabel et al., 2018)	n = 23 (20 females, 3 males), obese	12 weeks	Historical control	TRE: 8 h (10 am–6 pm) Control: AL	↓ Body weight and blood pressure ↔ Fat mass, fasting glucose, LDL cholesterol, TG
(Sutton et al., 2018)	n = 8 males, overweight	5 weeks	Cross-over	eTRE: 6 h (8 am–2 pm, dinner before 3 pm) Control: 12 h	↓ Fasting TG, desire to eat in the evening ↑ Insulin sensitivity, β cell responsiveness ↔ Body weight
(Jamshed et al., 2019; Ravussin, 2019)	n = 11 (4 females and 7 males), overweight	4 days	Cross-over	TRE: 6 h (8 am–2 pm) Control: 12 h (8 am–8 pm)	↓ Mean 24-h glucose, glycemic excursions, morning ghrelin, desire to eat ↑ Daytime EE, metabolic flexibility, fullness, plasma ketones
(Hutchison et al., 2019)	n = 15 males, overweight	1 week	Cross-over	eTRE: 9 h (8 am–5 pm) dTRE: 9 h (12 pm–9 pm) Baseline: AL	↓ Body weight, fasting TG, and hunger ↓ Mean fasting glucose by CGM in eTRE ↑ Glucose tolerance
(Tinsley et al., 2019)	n = 40 females, resistance trained	8 weeks	Randomized controlled	TRE: 8 h (12 pm–8 pm) TRE plus β-hydroxy β-methyl butyrate	↓ Fat mass ↑ Muscle performance
(Anton et al., 2019)	n = 10 (6 females, 4 males), overweight, ≥ 65 years	4 weeks	Within participant	TRE: 8 h Baseline: AL	↓ Body weight

**Table 1. List of Time-Restricted Eating Trials in Humans and Their Major Findings**

(Continued on next page)

Study	Participants	Trial length	Design	Intervention, Meal Time	Major Findings
(Wilkinson et al., 2019)	n = 19 (6 females, 13 males), overweight	12 weeks	Within participant	TRE: 10 h (self-selected, dinner before 8 pm) Baseline: ≥ 14 h	↓ Body weight, fat mass, waist circumference, blood pressure, plasma cholesterol ↔ Fasting glucose, HbA1c, HOMA-IR, fasting insulin
(Kesztyus et al., 2019)	N = 40 (31 females, 9 males), with abdominal obesity	3 months	Within participant	TRE: 8 -9 h Baseline: AL	↓ Waist circumference, HbA1c
(Parr et al., 2020)	n = 11 males, overweight	5 days	Cross-over	TRE: 8 h (10 am–6 pm) Extended eating: 15 h (7 am–10 pm)	↓ Night-time glucose, glucose and insulin iAUC after lunch ↔ Daytime glucose ↑ TG after lunch
(Chow et al., 2020)	N = 20 (17 females, 3 males), overweight	12 weeks	Randomized controlled	TRE: 8 h Non-TRE: AL	↓ Body weight, lean mass, and visceral fat mass.
(Gabel et al., 2020)	N = 14, overweight	12 weeks	Within participant	TRE: 8 h (10 am–6 pm) Baseline: AL	↓ Body weight, fat mass, systolic blood pressure ↔ Gut microbiome

**Table 1. Continued**

n, number; TRE, time restricted eating; RT, resistance trained; AL, ad libitum; IGF, insulin like growth factor; TG, triglycerides; LDL, low-density lipoprotein; EE, energy expenditure; SIRT1, sirtuin1; mTOR, mechanistic target of rapamycin; CGM, continuous glucose monitoring; eTRE, early TRE; dTRE, delayed TRE; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; iAUC, incremental area under the curve; ↓, reduced; ↑, increased; ↔, no change.

(Hutchison et al., 2019; Jamshed et al., 2019), although this was not universally observed (Wilkinson et al., 2019). TRE for 12 weeks did not alter gut microbiome in humans (Gabel et al., 2020).

Most of the studies performed in humans have observed a reduction in self-reported energy intake (Gabel et al., 2018; Gill and Panda, 2015; Wilkinson et al., 2019), which may account for some of the beneficial weight and health effects. However, in a highly controlled, cross-over feeding trial, 5 weeks of early (e) TRE (dinner before 3 pm) increased insulin sensitivity and  $\beta$  cell responsiveness and reduced oxidative stress as compared with the control condition in the absence of energy restriction and weight loss (Sutton et al., 2018), and increased fasting triglyceride as a physiological response to the increased fasting duration. Four days of eTRE (8 am–2 pm) also reduced fasting and postprandial glucose and increased daytime energy expenditure and the expression of *SIRT1*, clock genes, and genes involved in autophagy in blood (Jamshed et al., 2019; Ravussin, 2019). Five days of TRE (10 am–5 pm) also reduced night-time glucose in participants who were overweight (Parr et al., 2020). These studies suggest that TRE could be a promising tool for the improvement of metabolic outcomes in the general population.

### CHALLENGES IN TRANSLATING TRE TO HUMANS

TRE is a simple approach that could be highly beneficial in primary practice, since it does not require extensive nutrition knowledge or significant time commitment to convey to the patient in need, unlike current dietary practice guidelines (Australian Dietary Guideline, 2013). However, the majority of TRE interventions in animal models and in humans have been initiated early in the active phase (Chaix et al., 2014; Gabel et al., 2018; Gill and Panda, 2015; Hatori et al., 2012; Jamshed et al., 2019; Olsen et al., 2017; Ravussin, 2019; Sutton et al., 2018). Here, we discuss possible challenges with the translation of eTRE in the general population and the possible outcomes of delayed TRE (dTRE, i.e., allowing food consumption for identical time lengths late in the day).

Early morning is likely to be the optimal time to initiate TRE to maximize the metabolic benefits. For example, insulin sensitivity and glucose uptake are higher at the beginning of the active phase in nocturnal mice (Basse et al., 2018; Rudic et al., 2004) and diurnal humans (Sonnier et al., 2014). Similarly, lipid absorption in the intestine (Douris et al., 2011) and *de novo* lipogenesis in the liver are higher during the active phase in mice (Gilardi et al., 2014). Cholesterol and bile acid synthesis are also elevated early during the active phase (Chaix et al., 2014). Furthermore, findings from observational and epidemiological studies suggest that breakfast skippers are also more likely to be overweight, have poorer glucose control, and develop T2D as compared with people who identify as breakfast consumers (Bi et al., 2015). Although other observational studies have reported that skipping breakfast, without eating late, does not link to obesity, suboptimal glycemic control, or poorer metabolic health (Azami et al., 2019; Nakajima and Suwa, 2015; Okada et al., 2019). Women who were overweight were randomized to high-calorie breakfast versus high-calorie dinners, where the high-calorie breakfast group lost more body weight and had greater reductions in waist circumference, fasting glucose, and fasting insulin (Jakubowicz et al., 2013). In another study, individuals with T2D were provided with a three-meal-per-day diet (light dinner before 8 pm) or an isocaloric six-meal diet (heavy dinner and snacks continued until 11 pm) for 12 weeks. The three-meal diet reduced body weight, glycosylated hemoglobin, and therapeutic insulin dose and significantly lowered hyperglycemic episodes by continuous glucose monitoring. Clock gene expression in blood samples also showed higher oscillation in the three-meal diet (Jakubowicz et al., 2019). Eating breakfast and lunch only also reduced body weight, plasma glucose, and hepatic fat more than eating six meals spread throughout the day (Kahleova et al., 2014). Together, these studies show that consuming meals earlier in the day are optimal for weight control and improvements in glycemic profile under isocaloric conditions.

Implementing TRE early in the morning may be challenging in the general population both biologically and socially. There is large endogenous circadian variation in hunger, with peak in the evening and nadir in the morning (Qian et al., 2019; Scheer et al., 2013). This is because ghrelin, a hormone secreted by stomach that increases feelings of hunger, is under circadian regulation and is at biological nadir in the morning (Espelund et al., 2005) and peaks in the afternoon. Furthermore, family and communal get-togethers are essential factors to increase social bonding, feeling of physical and mental well-being, and overall happiness in humans. Group eating and food sharing are considered the easiest way to strengthen family and community bonds capable of providing social and emotional support (Dunbar,

2017). However, many social events are typically geared toward evening. Delaying the start time of TRE may overcome both of these issues, but the metabolic consequences of dTRE are not clear. As described earlier, fasting and feeding are known regulators of peripheral molecular clocks. Thus, it is likely that delaying TRE will delay peripheral clocks in metabolic organs. This was seen in recent human studies where skipping breakfast delayed *per* rhythms in adipose tissue (Loboda et al., 2009; Wehrens et al., 2017). However, whether there is a net consequence of a short phase delay in clocks on metabolic health in humans is currently unknown.

In athletes undertaking resistance training, dTRE (12-8 pm) reduced fat mass without altering fat-free mass and improved muscle performance (Tinsley et al., 2019). Blood glucose, insulin, total testosterone, and IGF-1 were also reduced in this study. However, severe time restriction, whereby all food intake was limited to one large daily meal eaten between 5 and 9 pm, impaired glucose tolerance in the following morning (Carlson et al., 2007). dTRE also failed to show any benefits in glycemic profile and body weight reduction when meal intake was limited to 4 h in the evening (anytime between 4 pm and midnight) for 4 days per week (Tinsley et al., 2017). However, the irregular patterning of meals in that study could also have contributed to this result (Farshchi et al., 2004).

Only two animal studies have directly compared eTRE with dTRE. In one study, mice underwent 6 h of TRE with HFD given either during the first half (ZT12-18) or second half (ZT18-24) of the night for 8 weeks. Body weight gain and insulin resistance as measured by HOMA-IR were higher in dTRE than in eTRE. However, both TREs equally improved glucose tolerance compared with *ad libitum* (Delahaye et al., 2018). The fasting length prior to the glucose assessment was not standardized in that study (7–16 h depending on intervention), which may have contributed to the results as glucose tolerance is higher after 18 h of fasting versus 6 h of fasting (Andrikopoulos et al., 2008). In another study, rats were fed for 12 h during night whether at ZT12-24 (eTRE) or ZT16-4 (dTRE) for 2 weeks. Despite similar caloric consumption, body weight gain was higher in the dTRE group and dTRE also delayed the phase of *clock*, *bmal1*, *per1*, *cry2*, and *rev-erba* by 2 h and that of *cry1* by 4 h in liver (Shimizu et al., 2018). The amplitudes of those genes were also lower in dTRE. However, the study was of short duration and did not include an *ad libitum* fed group. We conducted a preliminary study comparing dTRE with eTRE in men with obesity. This study showed that dTRE produced similar improvements in glucose tolerance as eTRE (Hutchison et al., 2019). However, when glycemic measurements were made by continuous glucose monitoring, only eTRE significantly reduced fasting glucose versus baseline. This reduction was at trend level for dTRE versus baseline, and there was no statistical difference in this improvement between TRE groups (Hutchison et al., 2019). The impact on clock genes was not examined. Larger trials comparing effects of eTRE versus dTRE are warranted.

Studies in mice have shown that the beneficial effects of TRE are dose dependent, with greater reductions in body weight, fat mass, and improvement in glucose tolerance when a 9-h protocol was implemented versus 12 and 15 h (Chaix et al., 2014; Sundaram and Yan, 2016). The optimal TRE time frame to recommend for people has not been tested. Clear improvements have been noted after 6-, 8-, 9-, and 10-h protocols (Gabel et al., 2018; Hutchison et al., 2019; Sutton et al., 2018; Wilkinson et al., 2019). It is likely that the greater time restriction would result in greater weight losses, which may maximize the metabolic benefits. However, very short feeding windows could also reduce adherence or result in poorer food choices, if the individual feels under too great a time pressure. Extending the eating window beyond 12 h is unlikely to have major beneficial metabolic effects (LeCheminant et al., 2013).

## CONCLUSION AND FUTURE DIRECTIONS

TRE initiated early in the active phase shows pleiotropic metabolic benefits in animal models of diet-induced obesity and aging. Short-term TRE trials in humans have shown modest reductions in body weight and improved cardio-metabolic health in people who are overweight or obese, suggesting that TRE may be a promising therapeutic tool. However, these studies are limited in number, sample size, and study duration. The feasibility of implementing early TRE in the general population on a daily basis is unclear, and the effects of delaying TRE to increase the potential translatability and acceptability of this dietary approach are unknown. Large-scale, long-term trials are warranted to determine if TRE is a viable alternative to current practice dietary guidelines.



## Resource Availability

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### Materials Availability

Not applicable.

### Data and Code Availability

Not applicable.

## AUTHOR CONTRIBUTIONS

P.R. searched the literature, and both authors contributed to data interpretation and preparation of the manuscript. L.K.H. had primary responsibility for the final publication.

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