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Escola de Educação Física, Fisioterapia e Dança

Programa de Pós-Graduação em Ciências do Movimento Humano

Dissertação de Mestrado

EFEITOS DA ALIMENTAÇÃO COM RESTRIÇÃO DE TEMPO EM DIFERENTES MOMENTOS DO DIA SOBRE A COMPOSIÇÃO CORPORAL E PARÂMETROS METABÓLICOS DE INDIVÍDUOS COM SOBREPESO E OBESIDADE GRAU 1

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Dissertação de Mestrado

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RESUMO

Introdução: As taxas de sobrepeso e obesidade têm aumentado em todo o mundo, e diversas abordagens nutricionais têm emergido para auxiliar no combate a este cenário. A alimentação com restrição de tempo (*Time-restricted eating* [TRE] em humanos) é um tipo de jejum intermitente que consiste em limitar a ingestão alimentar diária a um período de 4 a 12 horas, a fim de prolongar o tempo em jejum e alinhar o ciclo de alimentação-jejum aos ritmos circadianos. Estudos em modelos animais e, recentemente, em humanos apontam resultados promissores dessa abordagem dietética sobre o peso corporal e desfechos cardiometabólicos, sendo estes especialmente observados quando a janela de alimentação é destinada aos horários iniciais do dia (*early* TRE [eTRE]). Entretanto, pouco é conhecido sobre os efeitos crônicos do eTRE em comparação à TRE de início atrasado (*delayed* TRE [dTRE]) sobre o peso corporal e parâmetros de composição corporal e de saúde cardiometabólica em adultos com excesso de peso. Em adição, diversos estudos têm verificado uma restrição calórica não-intencional com a TRE, permanecendo desconhecido se os benefícios encontrados são devido à TRE ou à restrição calórica. **Objetivos:** Revisar a literatura atual acerca dos efeitos da TRE em humanos. Ainda, investigar, através de um ensaio clínico randomizado, os efeitos crônicos (8 semanas) da TRE em diferentes momentos do dia (eTRE *vs*. dTRE) e de uma dieta tradicional (controle), ambos sob restrição calórica, sobre o peso e composição corporal e parâmetros metabólicos em indivíduos com sobrepeso e obesidade grau 1. **Resultados:** Através da revisão narrativa observou-se que, embora em ascensão, há poucos estudos sobre o tema e variados protocolos de TRE têm sido adotados. Ainda assim, esta abordagem dietética apresenta efeitos benéficos como redução no peso corporal e melhorias em diversos biomarcadores, especialmente em indivíduos com excesso de peso. Através do ensaio clínico randomizado, não foram observadas diferenças estatisticamente significativas entre as intervenções eTRE, dTRE e dieta tradicional sobre peso, composição corporal e parâmetros cardiometabólicos após 8 semanas. **Conclusão:** Embora a literatura demonstre resultados promissores da TRE na saúde humana, especialmente quando a janela de alimentação é realizada no início do dia, no presente estudo experimental não foram encontradas diferenças significativas entre os protocolos de dieta tradicional, eTRE e dTRE sobre peso, composição corporal e marcadores de risco cardiometabólico em indivíduos com sobrepeso e obesidade, sob condições equivalentes de restrição calórica.

Palavras-chave: Jejum intermitente, Alimentação com restrição de tempo, Obesidade, Saúde Cardiometabólica.

ABSTRACT

Introduction: Overweight and obesity rates have increased worldwide, and several nutritional approaches have emerged to combat this scenario. Time-restricted eating (TRE) is an intermittent fasting type that consists of limiting the daily food intake to a period of 4 to 12 hours in order to prolong the fasting time and align the fasting-food cycle with circadian rhythms. Studies in animal models and, recently, in humans indicate promising results of this dietary approach on body weight and cardiometabolic outcomes, which are especially observed when the eating window is aimed at the early hours of the day (early TRE [eTRE]). However, little is known about the chronic effects of eTRE compared to delayed TRE (dTRE) on body weight, body composition and parameters of cardiometabolic health in overweight adults. Also, several studies have found unintentional energy restriction with TRE, and it remains unknown whether the benefits found are due to TRE or to energy restriction. **Objectives:** To review the current literature about the effects of TRE in humans. Also, to investigate, through a randomized clinical trial, the TRE chronic effects (8 weeks) at different times of the day (eTRE *vs.* dTRE) and a traditional diet (control), both under caloric restriction, on body weight, body composition and metabolic parameters in individuals with overweight and obesity grade 1. **Results:** Through the narrative review, it was observed that, although on the rise, there are few studies about the subject and various TRE protocols have been adopted. Nevertheless, this dietary approach has beneficial effects, such as reducing body weight and improvements in several biomarkers, especially in overweight individuals. Through the randomized clinical trial, no significant differences were observed between the eTRE, dTRE and traditional diet interventions on body weight, body composition and cardiometabolic parameters after 8 weeks. **Conclusion:** Although the literature shows promising results of TRE in human health, mainly when the eating window is performed at the beginning of the day, in this experimental study, no significant differences were found between the protocols of the traditional diet, eTRE and dTRE on body weight, body composition and cardiometabolic risk markers in individuals with overweight and obesity, under equivalent caloric restriction conditions.

Keywords: Intermittent fasting, Time-restricted eating, Obesity, Cardiometabolic health.

SUMÁRIO

1 APRESENTAÇÃO

A presente dissertação está composta por uma introdução geral, dois artigos (revisão narrativa e ensaio clínico randomizado) e considerações finais seguidas de perspectivas futuras sobre o tema da dissertação. O referencial teórico da dissertação está exposto através do artigo de revisão narrativa publicado na revista científica *Critical Reviews in Food Science and Nutrition*. Em seguida, será apresentado o artigo experimental referente ao ensaio clínico randomizado desenvolvido ao longo período de mestrado, o qual será submetido à revista *JAMA Internal Medicine.* Os dois manuscritos seguem incorporados ao documento no formato exigido pelo respectivo periódico.

Desta forma, a dissertação está apresentada da seguinte forma:

1) Capítulo I:

Introdução contendo aspectos relevantes sobre o tema e a justificativa para o desenvolvimento da pesquisa;

2) Capítulo II (artigo 1):

Artigo de revisão narrativa intitulado: "Time-Restricted Eating and Circadian Rhythms: The Biological Clock is Ticking" publicado na revista científica *Critical Reviews in Food Science and Nutrition (Impact Factor 2019: 7.862);*

3) Capítulo III (artigo 2):

Artigo original de pesquisa intitulado: "Cardiometabolic Effects of Early *vs.* Delayed Time-Restricted Eating on Adults with Overweight and Obesity: A Randomized Clinical Trial" que será submetido à revista científica *JAMA Internal Medicine (Impact Factor 2019: 18.652);*

4) Capítulo IV:

Considerações finais e perspectivas futuras.

CAPÍTULO I

2 INTRODUÇÃO

Os índices de sobrepeso e obesidade aumentam de forma alarmante na população mundial (GONZÁLEZ-MUNIESA et al., 2017; ROBERTO et al., 2015). Desde a década de 1970, a prevalência de obesidade aumentou em aproximadamente 300% em todo mundo (GONZÁLEZ-MUNIESA et al., 2017). Dados recentes da Organização Mundial da Saúde (OMS) apontam que, no mundo, mais de 1,9 bilhão de adultos estão acima do peso, dos quais mais de 650 milhões estão com obesidade (OMS, 2020). No Brasil, em 2019, cerca de 55,4% dos adultos estavam com sobrepeso e 20,3% com obesidade (BRASIL, VIGITEL, 2020). Segundo a OMS, o sobrepeso é classificado como índice de massa corporal (IMC) de 25 a 29,9 kg/m², enquanto classifica-se a obesidade como IMC ≥ 30 kg/m². Ainda, a obesidade é subdividida em grau I (IMC 30 a 34,9 kg/m²), grau II (IMC 35 a 39,9 kg/m²) e grau III (IMC ≥ 40 kg/m²) (OMS, 1998).

O excesso de peso sob a forma de gordura corporal está relacionado ao aumento do risco do desenvolvimento de doenças crônicas, como diabetes *mellitus* tipo 2, doenças cardiovasculares e câncer, além de mortalidade precoce (WILLIAMS et al., 2015). Diversos aspectos estão associados ao ganho de peso excessivo, incluindo fatores ambientais, psicológicos, biológicos e socioeconômicos (ROBERTO et al., 2015; WILLIAMS et al., 2015). O ganho de peso corporal é resultante de um desequilíbrio crônico entre o consumo e o gasto energético, em favor do primeiro, gerando um balanço energético positivo (MITCHELL et al., 2011). Fatores comportamentais como o estilo de vida sedentário (HEINONEN et al., 2013) aliado à alta ingestão de alimentos com baixa qualidade nutricional (POPKIN, ADAIR e NG, 2012) parecem estar entre as principais causas da crescente epidemia de obesidade (CHARANSONNEY e DESPRÉS, 2010).

Buscando reverter esse cenário, diversas abordagens nutricionais têm sido adotadas, incluindo o jejum intermitente (JI) (YANNAKOULIA et al., 2019). O JI é caracterizado pela submissão voluntária a períodos de privação alimentar, com redução ou ausência de ingestão energética intercaladas por períodos de maior consumo de alimentos e bebidas (LONGO E MATTSON, 2014). Em comparação às dietas com restrição calórica contínua, o JI parece promover benefícios similares na perda de peso corporal ou em parâmetros de saúde (TREPANOWSKI et al., 2017). Neste sentido, o JI tem sido frequentemente utilizado como uma alternativa às estratégias dietéticas convencionais (PATTERSON e SEARS, 2017). Estudos recentes apontam que diferentes tipos de JI podem melhorar a composição corporal e

desfechos cardiometabólicos, incluindo atenuação nos níveis plasmáticos de glicose e insulina, redução no peso e na pressão arterial, bem como melhora na sensibilidade à insulina e no perfil lipídico (FERNANDO et al., 2019; MENG et al., 2020; SANTOS e MACEDO, 2018). Dentre os principais protocolos de JI, destacam-se o regime de jejum modificado (ou dieta 5:2), o jejum de dias alternados e a alimentação com restrição de tempo (TRF; do inglês "*Time-Restricted Feeding"*) (PATTERSON e SEARS, 2017). A TRF consiste na ingestão alimentar diária limitada a um período de 4 a 12 horas, a fim de estender o tempo em jejum diário (DI FRANCESCO et al., 2018). Originalmente, essa estratégia não envolve alterações na qualidade ou na quantidade dos alimentos, apenas visa induzir um período robusto de jejum diário e alinhar o ciclo de alimentação-jejum aos ritmos circadianos endógenos, sincronizando a oferta de alimentos ao período em que o corpo está mais propício para recebê-los (DI FRANCESCO et al., 2018).

O sistema circadiano dos mamíferos é composto por um relógio central / mestre, localizado no núcleo supraquiasmático (NSQ) no hipotálamo, o qual controla diversos relógios periféricos, distribuídos pelo cérebro (extra-NSQ) e outros órgãos, incluindo fígado, músculo esquelético, tecido adiposo e pâncreas (ROENNEBERG e MERROW, 2016; STENVERS et al., 2019). Esse sistema coordena uma série de processos corporais que ocorrem ao longo do dia (ROENNEBERG e MERROW, 2016). O mecanismo molecular responsável pela geração dos ritmos circadianos nos relógios centrais e periféricos é baseado em ciclos de retroalimentação *(feedback)* negativa de transcrição e tradução, que ocorrem em praticamente todas as células do corpo humano (TAKAHASHI, 2017; STENVERS et al., 2019). Os ritmos gerados através deste mecanismo perduram por um período de aproximadamente 24 horas e, por isso, são denominados de circadianos (do latim *circa diem*, "cerca de um dia").

Os relógios centrais e periféricos geram ritmos autossustentados e autônomos, todavia estímulos externos *(zeitgebers)* podem alterar a sincronização circadiana (ROENNEBERG e MERROW, 2016). Assim, o comportamento do sistema circadiano é determinado pela complexa interação entre o relógio central, os relógios periféricos e os *zeitgebers* (ROENNEBERG e MERROW, 2016). Enquanto o relógio central é regulado principalmente pela presença de luz, os relógios periféricos são predominantemente responsivos à alimentação, especialmente a composição dos alimentos e o padrão temporal do consumo alimentar (ARBLE et al., 2009; LOGAN E MCCLUNG, 2019; REINKE E ASHER, 2019; STENVERS et al., 2019).

Evolutivamente, os humanos tornaram-se seres diurnos, estando ativos durante o dia e inativos no período noturno. Conforme exposto, desenvolveu-se um sistema circadiano endógeno para assegurar que processos fisiológicos sejam executados em momentos propícios ao longo do dia (STENVERS et al., 2019). A sociedade moderna tem apresentado comportamentos que contribuem para a cronodisrupção, a qual está relacionada ao desenvolvimento de eventos adversos à saúde, como resistência à insulina, diabetes *mellitus* tipo 2 e obesidade (JIANG e TUREK, 2018; LOGAN e MCCLUNG, 2019; SCHEER et al., 2009; STENVERS et al., 2019). Dentre os comportamentos prejudiciais ao bom funcionamento do sistema circadiano estão a exposição excessiva à luz artificial, o *jetlag* social, a prática de trabalhos de turnos, bem como o consumo em demasia e ininterrupto de alimentos, especialmente aqueles de alta densidade energética e baixa qualidade nutricional (JIANG e TUREK, 2018; STENVERS et al., 2019). Tendo em vista que o desenvolvimento de doenças metabólicas pode ser acentuado quando os ritmos circadianos endógenos estão fora de sincronia com os estímulos externos, otimizar a sincronização entre eles pode minimizar a prevalência e o ônus das doenças cardiometabólicas (JIANG e TUREK, 2018; STENVERS et al., 2019).

Nos últimos anos, através da crononutrição, passou-se a investigar a complexa relação entre nutrição, metabolismo e sistema circadiano, pois além da qualidade e da quantidade dos alimentos, o momento do consumo alimentar parece ser um ponto crítico para desfechos em saúde (ALMOOSAWI et al., 2016; ASHER E SASSONE-CORSI, 2015). Diversos processos metabólicos relacionados à alimentação apresentam maior desempenho pela manhã em comparação à tarde e à noite, tais como tolerância à glicose, sensibilidade periférica à insulina, responsividade das células β-pancreáticas, efeito térmico dos alimentos, além de oxidação de ácidos graxos no músculo esquelético. Embora haja uma otimização do metabolismo humano para o consumo alimentar nas primeiras horas do dia em comparação às últimas (POGGIOGALLE, JAMSHED e PETERSON, 2018; STENVERS et al., 2019), populações de diversos países têm apresentado elevado consumo calórico no período noturno (ALMOOSAWI et al., 2016). Estudos verificaram que destinar o maior consumo energético diário à primeira parte do dia culmina em efeitos positivos na saúde, incluindo maior perda de peso e menor resistência à insulina (GARAULET et al., 2013; JAKUBOWICZ et al., 2013). Além disso, ingerir uma maior quantidade de calorias no início do dia e manter períodos consistentes de jejum noturno foi uma estratégia proposta em estudos recentes, a fim de atenuar o risco de complicações cardiometabólicas (ST-ONGE et al., 2017; STENVERS et al., 2019).

Induzir um ciclo robusto de alimentação-jejum, limitando a ingestão energética a um período específico do dia e mantendo um período de jejum adequado, parece ser determinante para aprimorar parâmetros metabólicos e atenuar a cronodisrupção e seus efeitos deletérios (ADAMOVICH et al., 2014; CHAIX et al., 2014; SUTTON et al., 2018). Em modelos animais foram verificados inúmeros efeitos positivos da TRF, tais como redução do colesterol plasmático e da glicemia em jejum, atenuação do peso e da gordura corporal, da disbiose e da inflamação, bem como melhora no padrão do sono e da função cardíaca (LONGO E PANDA, 2016). Foi previamente observado que roedores noturnos expostos a dietas ricas em gorduras durante sua fase inativa (ou seja, diurna) apresentaram ganho de peso significativamente maior, em comparação àqueles que se consumiam a mesma dieta na fase ativa habitual (noturna) (ARBLE et al., 2009; HATORI et al., 2012). Em estudo prévio, verificou-se que camundongos submetidos a uma dieta rica em gorduras *ad libitum* ganharam peso e desenvolveram uma série de distúrbios metabólicos, como esteatose hepática, dislipidemia e intolerância à glicose. Em contraste, àqueles que consumiram uma dieta rica em gorduras por um período delimitado (9-10 horas) durante a fase noturna / ativa não apresentaram tais complicações (CHAIX et al., 2018). Esses resultados sugerem que, em modelos animais, restringir o tempo de alimentação a um determinado período dentro da fase biológica ativa, em comparação ao consumo *ad libitum*, pode atenuar os prejuízos metabólicos induzidos por uma dieta hiperlipídica. Além disso, tais achados parecem ocorrer independentemente de modificações no balanço energético, no peso corporal ou na qualidade da dieta (HATORI et al., 2012; CHAIX et al., 2014; CHAIX et al., 2018; SMITH et al., 2019). Diante destas observações promissoras em animais, os efeitos dessa estratégia alimentar no metabolismo humano passaram a ser recentemente investigados.

Gill e Panda (2015) analisaram pela primeira vez os impactos da *time-restricted eating* (TRE) em adultos norte-americanos. Oito homens com excesso de peso tiveram sua alimentação reduzida a uma faixa auto selecionada de 10-11 horas / dia. Após 16 semanas, houve melhora no padrão de sono e perda de peso corporal, a qual foi mantida durante um ano. A aplicação do protocolo de TRE levou, de forma involuntária, a uma redução na ingestão energética diária, advinda especialmente da redução no consumo de bebidas alcoólicas e lanches noturnos (GILL e PANDA, 2015). Corroborando com este achado, uma série de outros estudos demostraram que o encurtamento da janela alimentar induzido pela TRE culminou em uma redução não-intencional no consumo energético, impossibilitando atribuir quaisquer benefícios encontrados diretamente ao aumento do jejum diário (ANTONI et al. 2018; CIENFUEGOS et al., 2020; GABEL et al., 2018; WILKINSON et al., 2020). Em vista desses

achados, Stratton et al. (2020) compararam os efeitos da TRE aos da dieta tradicional, ambas sob condições equivalentes de déficit calórico, em homens recreacionalmente ativos. Após quatro semanas de dieta hipocalórica e hiperproteica associada ao treinamento de força, não foram encontradas diferenças significativas entre os grupos em parâmetros de composição corporal, desempenho muscular e biomarcadores plasmáticos (STRATTON et al., 2020). Sendo assim, não está claro se os efeitos benéficos da TRE observados em humanos são oriundos da restrição energética, da perda de peso corporal ou da delimitação de um período de alimentação.

Sutton et al. (2018) realizaram um estudo *crossover* utilizando um subtipo de TRE, denominada *early* TRE (eTRE). Nesta condição, a janela de alimentação dos participantes era de 6 horas (8:00 às 14:00), enquanto na condição controle a mesma era de 12 horas (8:00 às 20:00). A fim de verificar se existiam benefícios intrínsecos da TRE, oito homens de meia-idade com pré-diabetes e obesidade consumiam uma dieta isocalórica para manutenção do peso corporal por cinco semanas em cada condição. Em comparação à condição controle, foram observados efeitos positivos da TRE na sensibilidade à insulina e na responsividade das células β-pancreáticas, além de reduções nos níveis de insulina plasmática e de pressão arterial. Assim, demonstrou-se que o subtipo de TRE utilizado, ao restringir a alimentação à primeira metade do dia, promove melhorias em diversos parâmetros metabólicos, independentemente de reduções no consumo alimentar e no peso corporal (SUTTON et al., 2018). Nesta perspectiva, o momento do dia em que a janela de alimentação ocorre surgiu como um possível contribuinte da magnitude dos resultados obtidos com a TRE. No entanto, em humanos, apenas um estudo comparou diretamente os efeitos da eTRE (8:00 às 17:00) com a TRE de início atrasado (*delayed* TRE [dTRE]; 12:00 às 21:00), não sendo observada diferenças significativas entre as condições nas respostas glicorregulatórias a uma refeição padrão ou no perfil de glicose de 24 horas. Contudo, este estudo *crossover* foi realizado apenas em homens de meia-idade com obesidade e cada condição de TRE durou apenas sete dias (HUTCHISON et al., 2019). Desta forma, permanecem desconhecidos os efeitos crônicos da eTRE em comparação à dTRE em adultos com obesidade.

Tendo em vista o exposto, os objetivos do presente trabalho são (1) apresentar, por meio de uma revisão narrativa, o cenário atual sobre os estudos envolvendo TRE em humanos, bem como (2) investigar, através de um ensaio clínico randomizado, os efeitos crônicos de diferentes abordagens de TRE (eTRE e dTRE) e de um protocolo de dieta tradicional (controle), ambos em condição de restrição calórica, sobre o peso, a composição corporal e parâmetros metabólicos em indivíduos com sobrepeso e obesidade grau 1.

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CAPÍTULO II

3 ARTIGO 1

Time-Restricted Eating and Circadian Rhythms: The Biological Clock is Ticking

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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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

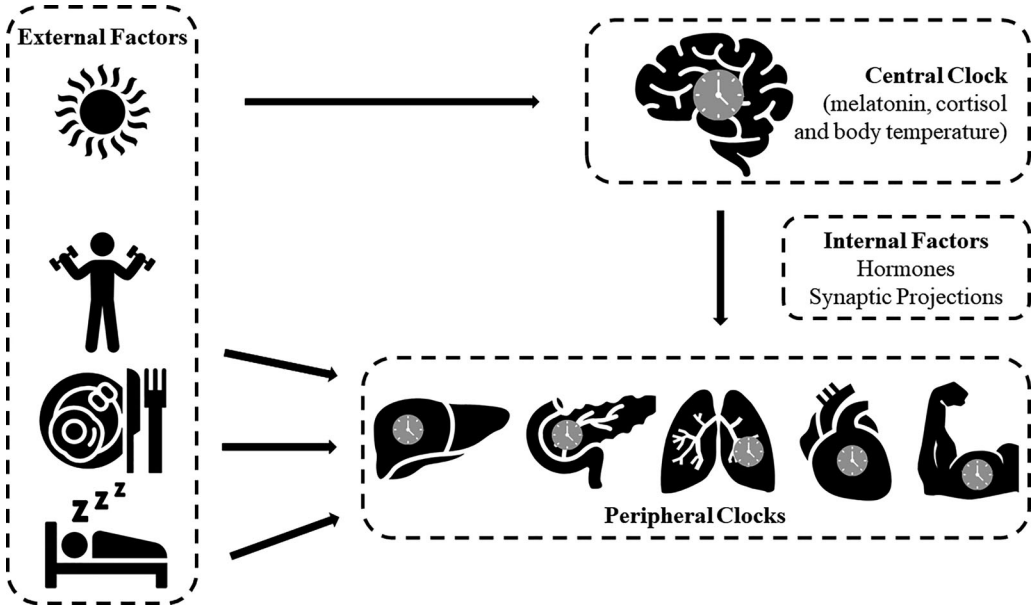

Figure 1. The circadian system is composed by a central clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and a series of peripheral clocks located in various organs of the body. Central clock is regulated mainly by light, while the peripheral clocks are regulated especially by 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.

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CAPÍTULO III

4 ARTIGO 2

Cardiometabolic Effects of Early vs. Delayed Time-Restricted Eating in Adults with Overweight and Obesity: A Randomized Clinical Trial.

Title Page

Manuscript title:

Cardiometabolic Effects of Early *vs.* Delayed Time-Restricted Eating in Adults with Overweight and Obesity: A Randomized Clinical Trial.

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Title

Cardiometabolic Effects of Early *vs.* Delayed Time-Restricted Eating in Adults with Overweight and Obesity: A Randomized Clinical Trial

Key Points

Question: What is the chronic effect of early *vs.* delayed time-restricted eating on body weight, body composition, and cardiometabolic health in adults with overweight and obesity?

Findings: In this 8-week randomized clinical trial, no significant differences were found between early *vs.* delayed time-restricted eating on body weight, body composition, and metabolic markers of adults with overweight and obesity.

Meaning: Time-restricted eating with caloric deficit, regardless of the time of day, promotes body weight loss and cardiometabolic benefits in individuals with overweight and obesity.

Abstract

Importance: The chronic effects of early and delayed time-restricted eating, directly compared, on body weight, body composition, and cardiometabolic health remain unknown in humans.

Objective: To compare effects of early and delayed time-restricted eating on body weight, body composition, and cardiometabolic parameters in adults with overweight and obesity.

Design: 8-week randomized clinical trial with three parallel groups.

Setting: This study was conducted between September 2019 and May 2020 at Federal University of Rio Grande do Sul in Porto Alegre, Brazil.

Participants: Females and males (20 to 40 years) with overweight and obesity.

Interventions: Participants were randomized to 1 of 3 groups for 8 weeks: early time-restricted eating (eTRE; 8-h eating window; 8:00-16:00), delayed time-restricted eating (dTRE; 8-h eating window; 12:00-20:00), or a control group (12-h eating window; 8:00-20:00). All groups were prescribed a 25% energy deficit relative to daily energy requirements. Participants were instructed to eat three structured meals per day in the eating window.

Main Outcomes and Measures: Body weight, body composition, and cardiometabolic parameters were measured at 0 and 8 weeks.

Results: A total of 48 adults with overweight and obesity were recruited, and 37 completed the study (mean [SD] age, 30 [6] years; body mass index, 30.5 [2.7] kg/m²). After the interventions, there was no significant difference between the three diet protocols for any of the outcomes. Compared to baseline, significant decreases were observed in body weight (eTRE group: -4.15 kg; 95% CI, -5.57 kg to -2.73 kg; dTRE group: -4.80 Kg; 95% CI, -5.90 kg to -3.70 kg; control group: -4.00 kg; 95% CI, -5.90 kg to -2.10 kg), fasting glucose levels (eTRE group: -4.41 mg/dL; 95% CI, -8.06 mg/dL to -0.76 mg/dL; dTRE group: -2.42 mg/dL; 95% CI, -8.13 mg/dL to 3.29 mg/dL; control group: -3.47 mg/dL; 95% CI, -8.50 mg/dL to 1.56 mg/dL), and fasting insulin levels (eTRE: -9.40 µIU/mL; 95% CI, -13.74 µIU/mL to -5.07 µIU/mL; dTRE: -4.15 µIU/mL; 95% CI, -8.83 µIU/mL to 0.53 µIU/mL; control group: -8.09 µIU/mL; 95% CI, -16.09 µIU/mL to -0.10 µIU/mL).

Conclusions and Relevance: Time-restricted eating with a caloric deficit, regardless of the time of day, promotes cardiometabolic benefits in individuals with overweight and obesity. Moreover, these effects are not superior to those produced by traditional energy restriction without a time-restricted eating window.

Trial Registration clinicaltrials.gov Identifier: NCT04647149.

Introduction

The prevalence of obesity has increased dramatically across the world[1]. This condition is related to a higher risk for cardiovascular and metabolic diseases, premature mortality, and a health-related financial burden[1]. In response, several nutritional strategies have been used to mitigate this scenario and its complications[2]. Intermittent fasting has emerged as an alternative to traditional dietary approaches[3], with extension of fasting periods showing positive effects on body weight and metabolic parameters, especially in adults with overweight[4].

Time-restricted eating (TRE) is a type of intermittent fasting that aims to reduce the daily eating window (~4 to 12 hours) and to extend the duration of the daily fasting period[5]. This approach, aligned with the active biological phase, improves health outcomes, regardless of energy restriction, weight loss, or quality of diet in rodents[6,7]. In humans, prior studies demonstrated that TRE, through decreasing the eating window, can produce an unintentional reduction in energy intake and result in body weight loss and benefits in metabolic parameters[8–11]. In this sense, it is unclear whether the positive effects observed in humans occur due to caloric restriction, even if unintentional, or by TRE *per se*[12]. A subtype of this nutritional strategy, known as early TRE (eTRE), primarily limits food intake to the early hours of the day, in order to align eating with the human body's circadian rhythms[13].

The circadian system controls metabolism in a cycle of approximately 24 hours, orchestrating numerous metabolic events[14]. Several of these processes function optimally in the morning, including insulin sensitivity, glucose tolerance, and the thermic effect of food[15]. Thus, food intake out of synchrony with circadian rhythms (e.g., a delayed and prolonged eating schedule) seems to promote negative impacts on health, including increased obesity risk and cardiometabolic impairments[16,17].

As typically implemented, the delay at the beginning of eating could mitigate the beneficial effects of TRE on metabolic health[18]. Nevertheless, only one study has directly compared the effects of eTRE *vs*. delayed TRE (dTRE), with similar findings between protocols[19]. However, this study was performed exclusively in men and each TRE condition lasted only seven days[19]. The present study aimed to compare the chronic effects of eTRE, dTRE, and traditional (control) diet protocols on body weight, body composition, and risk indicators for cardiometabolic disease in adults with overweight and obesity. We hypothesized that the eTRE group would present greater benefits in cardiometabolic parameters, especially in glucose metabolism, compared to the dTRE and control groups.

Methods

Study Design and Participants

The study was a single-center, parallel-group, randomized trial, performed between September 2019 and May 2020 at the Federal University of Rio Grande do Sul, Brazil. The study was previously approved by the local Research Ethics Committee (nº 3.525.665) and was conducted in accordance with the Declaration of Helsinki. This trial was registered at clinicaltrials.gov as NCT04647149. Recruitment was continuous by social media and flyers placed around the university, and the first participant signed the consent form on 3 September 2019. Participation in the study was voluntary and did not involve any payment.

More than 600 people expressed interest in the study. Thus, pre-screening through a cell phone interview was performed. Based on this pre-screening, eligible participants were scheduled for a screening visit at the laboratory in the morning after overnight fasting. At this visit, participants provided oral and written informed consent to the principal researcher. After an admission interview, evaluations of height and body weight to calculate body mass index, resting metabolic rate to calculate energy intake, and resting blood pressure occurred. Additionally, a blood collection was conducted to assess fasting plasma glucose and triglycerides levels.

Eligible participants (detailed eligibility criteria described in eMethods in Supplement 1) who provided consent were scheduled for a second visit within two weeks of the initial screening visit. Participants arrived at the laboratory between 6:30 and 8:00 after overnight fasting. First, body weight, resting metabolic rate, respiratory exchange ratio, and body composition were measured. After these assessments, a fasting capillary and venous blood collection and a 2-hour oral glucose tolerance test (OGTT) were performed. Subsequently, the participants consumed a standard meal consisting of sandwich bread and mozzarella cheese (~250 Kcal, 27 g of carbohydrate, 11 g of protein and 11 g of fat). After approximately 30 minutes, they performed a maximum effort test on a cycle ergometer. During this visit, physical activity levels, chronotype, risk of binge eating, appetite parameters, and sleep pattern were assessed. The measures of resting metabolic rate, respiratory exchange ratio, peak oxygen consumption, chronotype, appetite parameters, sleep pattern, and risk of binge eating disorder are described in eMethods in Supplement 1. Participants were instructed to maintain their usual physical activity levels throughout the trial (analysis of physical activity levels are described in eMethods in Supplement 1). After the first month of study, participants returned to the laboratory for a nutritional consultation. All assessments were performed before and after the intervention period. eFigure 1 presents the study protocol with the experimental design (eFigure 1a).

Randomization

Participants were randomized in a 1:1:1 ratio to eTRE group, dTRE group, or control group. Randomization was performed by an independent researcher using an automatic randomizer (https://www.randomizer.org/) and was stratified by sex and body mass index. Allocations were concealed until pre-intervention measures were complete. The study staff assisting with data collection remained blinded regarding the allocation of participants. Due to the nature of the study, the principal researcher and the participants were not blinded during the intervention.

Dietary Interventions

Participants were prescribed a diet to promote weight loss. Energy intake was calculated as resting metabolic rate multiplied by the physical activity level of 1.4 minus 25% of the daily energy requirements. Diets were formulated to contain 50% energy as carbohydrate, 20% as protein, and 30% as fat. Participants were instructed to divide their daily energy intake between three meals each day, and snacks between meals were not allowed. Outside the eating window, water and noncaloric and unsweetened beverages, such as coffee, tea, yerba mate (*Ilex paraguariensis*), sparkling or still water were allowed as a tool to increase compliance. Beverages with artificial sweeteners were not allowed during this period. The only difference between the three groups was the duration and the timing of the eating window. The eTRE group was instructed to eat from 08:00 until 16:00 (8-hour window), while the dTRE group to eat from 12:00 until 20:00 (8-hour window), and the control group to eat from 08:00 until 20:00 (12-hour window) (eFigure 1b). Detailed dietary interventions described in eMethods in Supplement 1.

Outcome Measures

Body Weight and Body Composition

Body weight was measured via a digital scale with the participants fasted and wearing light clothes. Body composition (total mass, fat-free mass, fat mass, % fat and bone mineral content of the whole body, trunk, arms, and legs) was estimated by dual-energy x-ray absorptiometry (Prodigy Primo, GE Healthcare, USA). The same evaluator conducted all assessments. Detailed body composition assessment is described in eMethods in Supplement 1.

Biochemical Measures

Blood samples were obtained following a 12-hour overnight fast to analyze the levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, triglycerides, β-hydroxybutyrate, glucose, and insulin. The blood collection was conducted by the same experienced evaluators. 2-h OGTT was performed after fasting blood collection. Indices of insulin sensitivity (QUICKI and Matsuda), insulin resistance (HOMA-IR), and β-cells functional capacity (HOMA-β) were calculated (detailed blood collection and analysis described in eMethods in Supplement 1).

Assessment of Food Compliance

After the interventions, food compliance was verified in two ways. Participants were considered adherent when their energy intake, determined via three 3-day food records (collected pre-intervention and after 4 and 8 weeks of the intervention), was between 80 to 100% of their prescribed daily energy goal, while adherence to the eating window was analyzed by the time of sending photos of meals. Firstly, the participants who sent > 70% of the photos of the meals during the 56 days (8 weeks) were considered adherent to sending photos. Of these, those who have completed the eating window period at the correct time (see Dietary Interventions in eMethods in Supplement 1) were considered totally adherent. However, we do not exclude non-adherent participants from the analyses. The diet of the participants and their food records were calculated using the nutritional software *Dietwin Plus*®.

Statistical Analysis

The software G*Power 3.1.9. was used for the sample size calculation of the present study. Due to the absence of previous studies comparing the chronic effects of TRE at different times (early *vs.* delayed) when this study was designed, we adopted a moderate effect size (d Cohen 0.50), as well as a significance level (α) of 0.05 and a power (β) of 80%. Considering an attrition rate of 20%, the required sample size was 51 participants (n=17 / group). Data were analyzed by a Generalized Estimating Equations model using main effects (group and time) and interaction (group*time). A Bonferroni post hoc test was used to detect differences. An unstructured working correlation matrix was employed. Analyses were performed for those who started the study (intention-to-treat) and also for those who completed the study and had all data available (per protocol). Generalized Estimating Equations can handle missing values within the model; therefore, no data imputation was performed for the intention-to-treat analysis[20]. All data are presented as mean (95% confidence interval, CI) unless otherwise indicated. Statistical analysis was performed in IBM SPSS version 18, and $p < 0.05$ was considered statistically significant.

Results

Participant Characteristics and Attrition

Seventy-four participants were screened and attended the first laboratory visit. A total of 48 (65%) were randomized to the TRE groups or control group, and 37 (77%) completed the study (Figure 1). The dropout rate was higher in the dTRE group (31%; 5 of 16) compaed to the eTRE and control groups (19%; 3 of 16 for both). However, only in the eTRE group dropouts were due to the eating window period (self-reported). Baseline characteristics of the participants are shown in table 1. Participants were primarily women (84%) with grade I obesity (mean age 30 [SD 6] years, body index mass 30.5 [SD 2.7] kg/m^2). All results are presented in table 2 (per protocol) and supplementary table 1 (intention-to-treat). Results presented in text and figures in the following sections refer to the per protocol analysis unless otherwise stated.

Body Weight and Body Composition

There was a significant decrease in body weight and body composition parameters at week 8 for TRE and control groups, with no significant difference between protocols. There was a body weight loss of -4.15 kg (95% CI, -5.57 kg to -2.73 kg), -4.80 kg (95% CI, -5.90 kg to -3.70 kg) and -4.00 kg (95% CI, -5.90 kg to -2.10 kg) for the eTRE, dTRE and control group, respectively (Figure 2a). Fat mass decreased in the eTRE (-2.90 kg; 95% CI, -3.92 kg to -1.87 kg), dTRE (-3.58 Kg; 95% CI, -4.63 kg to -2.52 kg), and control (-3.04 kg; 95% CI, -4.30 kg to -1.79 kg) groups (Figure 2b). Fat-free mass decreased in the eTRE group (-1.24 kg; 95% CI, -1.94 kg to -0.55 kg), dTRE group (-1.22 kg; 95% CI, -1.76 kg to -0.68 kg), and control group (-0.95 kg; 95% CI, -1.73 kg to -0.18 kg) (Figure 2c). A significant loss in fat-free mass and fat mass in all body segments was observed, as well as a reduction in bone mineral content in the trunk (Figure 2d, Table 2; eTable 1).

Cardiometabolic Parameters

There were significant reductions in fasting glucose and insulin levels at week 8 for the three groups, with no significant difference between them. A decrease in fasting glucose levels of -4.41 mg/dL (95% CI, -8.06 mg/dL to -0.76 mg/dL), -2.42 mg/dL (95% CI, -8.13 mg/dL to 3.29 mg/dL), and -3.47 mg/dL (95% CI, -8.50 mg/dL to 1.56 mg/dL) were verified for eTRE, dTRE and control groups, respectively (Figure 3a). Likewise, fasting insulin levels decreased -9.40 µIU/mL (95% CI, -13.74 µIU/mL to -5.07 µIU/mL), -4.15 µIU/mL (95% CI, -8.83 µIU/mL to 0.53 µIU/mL), and -8.09 µIU/mL (95% CI, -16.09 µIU/mL to -0.10 µIU/mL) for eTRE, dTRE and control groups, respectively (Figure 3b). A significant decrease in insulin resistance, measured by HOMA-IR, as well as in the functional β-cell capacity, measured by HOMA-β, was verified, without a significant difference

between the groups (Figure 3c and 3d). Additionally, there was a significant increase in insulin sensitivity (measured by QUICKI) with no difference between groups. No significant difference in the mean glucose concentration of the 2-h OGTT and in the insulin sensitivity, measured by Matsuda Index, was verified after the intervention or between groups. There was a significant decrease in fasting plasma concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and non-high-density lipoprotein cholesterol, with no difference between groups (eFigure 2). No significant difference in fasting triglycerides concentrations was verified after intervention or between groups. There was a significant increase in the blood concentration of β-hydroxybutyrate, without significant differences between groups.

Energy Metabolism

There was a significant decrease in resting metabolic rate and in respiratory exchange ratio, over time, regardless of group. No significant difference in peak oxygen consumption was observed after the intervention or between groups (Table 2).

Subjective Parameters

Parameters of appetite, sleep quality and the risk of binge eating results are shown in table 2. Intention-to-treat analysis revealed a group x time interaction for subjective feelings of hunger and satiety (eTable 1). There was a significant decrease in hunger in both TRE groups and an increase in the control group. For satiety, there was a reduction in the control group and an increase in the eTRE group. The other results of the intention-to-treat analysis did not substantively differ from the per protocol analysis (eTable 1).

Food Compliance

Dietary data are presented in supplementary table 3 (eTable 3). The 3-day food records showed that the participants consumed significantly fewer calories during the study compared to their usual intake and the prescribed diet (eTable 3). Additionally, eTRE group consumed significantly less protein than the other groups in the fourth week of the intervention but not in the eighth week. Regarding the eating window, only two participants from each group did not send > 70% of the photos of their meals, and only one participant in the dTRE group did not meet the correct time of the eating window (13:42 until 21:27). For totally adherents, the average eating window was 7:55 hours (8:46 until 16:41) for the eTRE group, 7:49 hours (12:37 until 20:27) for the dTRE group, and 11:44 hours (8:38 until 20:23) for the control group.

No significant change in the levels of physical activity throughout the study was observed (eTable 2).

Discussion

In the present study, no unique benefits of early or delayed 8-hour TRE were observed, relative to a control group with a 12-hour eating period, when all groups were prescribed an energy deficit and consumed three meals per day. Therefore, our results suggest that, with caloric restriction, TRE and traditional diet protocols can promote similar benefits for body weight, body composition and metabolic parameters. Previous studies have demonstrated several positive effects of distinct TRE protocols, especially in populations with overweight and obesity[8–10,13,21]. TRE does not always involve intentional calorie restriction or changes in diet quality[5], but this approach often produces an unintentional reduction in energy intake of ~20 to 30%[8–10]. Thus, it remains unclear what proportion of the benefits attributed to TRE occur due to prolonged daily fasting, involuntary energy restriction, and weight loss[12]. In this sense, we chose to prescribe a similar calorie-restricted diet (~25%) to TRE and control groups to assess the possible benefits of these diet protocols under isocaloric conditions. Our dietary analysis indicated energy consumption lower than prescribed in all groups, which possibly explains the more pronounced reductions in body weight as compared to previous studies of TRE[8–11,21]. However, it is known that people with obesity often underreport caloric intake when completing food records[22], indicating a limitation of investigations using this method in free-living individuals.

Sutton et al. found several cardiometabolic benefits in eight middle-aged men with pre-diabetes after 5 weeks of eTRE compared to a control condition[13]. Similar to previous observations in rodents[6], positive findings occurred regardless of calorie restriction or weight loss. However, our findings do not corroborate these unique benefits of eTRE as we did not find superior effects of eTRE as compared to other groups. However, the stricter protocol of eTRE and clinical condition of the participants may explain these divergent findings. Additionally, eTRE and dTRE were not compared in the investigation of Sutton et al.[13]. To our knowledge, only one study directly compared the effects of eTRE and dTRE in adults with obesity to date[19]. In a 1-week crossover study with fifteen middle-aged men, Hutchinson et al. reported no differences between TRE conditions for most biomarkers. However, eTRE significantly reduced mean overnight fasting glucose concentrations compared to baseline, without differences between TRE protocols[19]. These results are similar to those of the present study since we observed benefits in both TRE groups with a slight but not significant improvement in eTRE compared to dTRE for glucose metabolism. Despite the promising results found in our study and in others[13,19,23,24], so far, there is little evidence to indicate a definitive superiority of eTRE compared to dTRE for human health.

In the present study, mean reductions in fat-free mass corresponded to approximately 25% of weight loss. This finding is contrary to a recent study, which found significant lean mass reductions, corresponding to ~65% of weight loss, in middle-aged adults with obesity after 12 weeks of TRE (8-h eating window; 12:00 to 20:00) compared to an unrestricted-time diet[25]. Recent studies have highlighted the importance of adequate protein intake while adhering to a TRE diet to mitigate unwanted losses in lean mass[25–28]. In our study, although the eTRE group consumed significantly less protein than the other groups in the fourth week, there was no difference at other timepoints. Therefore, the generally similar protein intakes among groups may have contributed to the similar fat-free mass decreases at the end of the intervention.

Contrary to our findings, Jones et al. showed an improvement in whole-body insulin sensitivity in healthy and physically active men after two weeks of eTRE, regardless of changes in body composition[29]. Additionally, after our diet interventions, similar to Sutton et al.[13], differences in mean glucose concentrations during the OGTT were not observed. Our participants' low physical activity level and, consequently, the lower glucose uptake by skeletal muscle may explain the lack of benefits[30,31]. Moreover, the participants in the present study had obesity but were also generally healthy, which could have mitigated improvements in health outcomes. Nevertheless, additional improvements in most cardiometabolic risk indicators were observed for all diet protocols.

To the authors' knowledge, the present study is the first to directly compared the chronic effects of eTRE *vs*. dTRE, as well as to implement both TRE and a control eating schedule with the same degree of energy restriction in adults with overweight and obesity. Both TRE protocols induced an important and clinically relevant weight loss of ≥ 5% on average over 8 weeks, without compromising fat-free mass beyond the loss seen in the control group and expectations for energy-restricted diets. Moreover, positive effects were noted for fasting blood lipids, glucose and insulin levels, insulin resistance, and insulin sensitivity indices. Thus, this type of intermittent fasting, regardless of the time of day, is as effective as a traditional calorie-restricted diet to promote weight loss and cardiometabolic benefits. Although our findings are promising, future studies are needed to examine whether the body weight loss and cardiometabolic benefits observed in this trial with early and delayed TRE can be sustained in the long-term and whether they occur in distinct populations.

Limitations

The present study has limitations. First, the duration of trial was short, and the viability of this intervention needs to be investigated in the long term (e.g., 6 – 12 months). Second, since the dropout rate in dTRE group was higher than expected, our power to detect differences between groups decreased. Third, we did not control the

menstrual cycle phase for more consistent comparisons of the biomarkers analyzed. Finally, we did not comprehensively investigate the occurrence of adverse effects. However, no participant reported any serious adverse effects during the study. Mild adverse events, such as hunger and headaches, were reported to the research team, especially in the first weeks of the study in both TRE groups, suggesting that mild adverse effects may occur at the onset of TRE, but they tend to disappear over time.

Conclusion

In this randomized clinical trial, under caloric restriction conditions, 8 weeks of eTRE, dTRE and traditional diet protocols promote similar improvements of body weight, body composition, and cardiometabolic parameters in individuals with overweight and obesity.

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Drafting of the manuscript: All authors.

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Conflict of Interest Disclosures: GMT previously served as a scientific consultant for a phone application that allows users to monitor their usage of intermittent fasting programs; this consultancy consisted of providing evidence-based information regarding intermittent fasting. The authors remaining have no conflicts of interest to declare.

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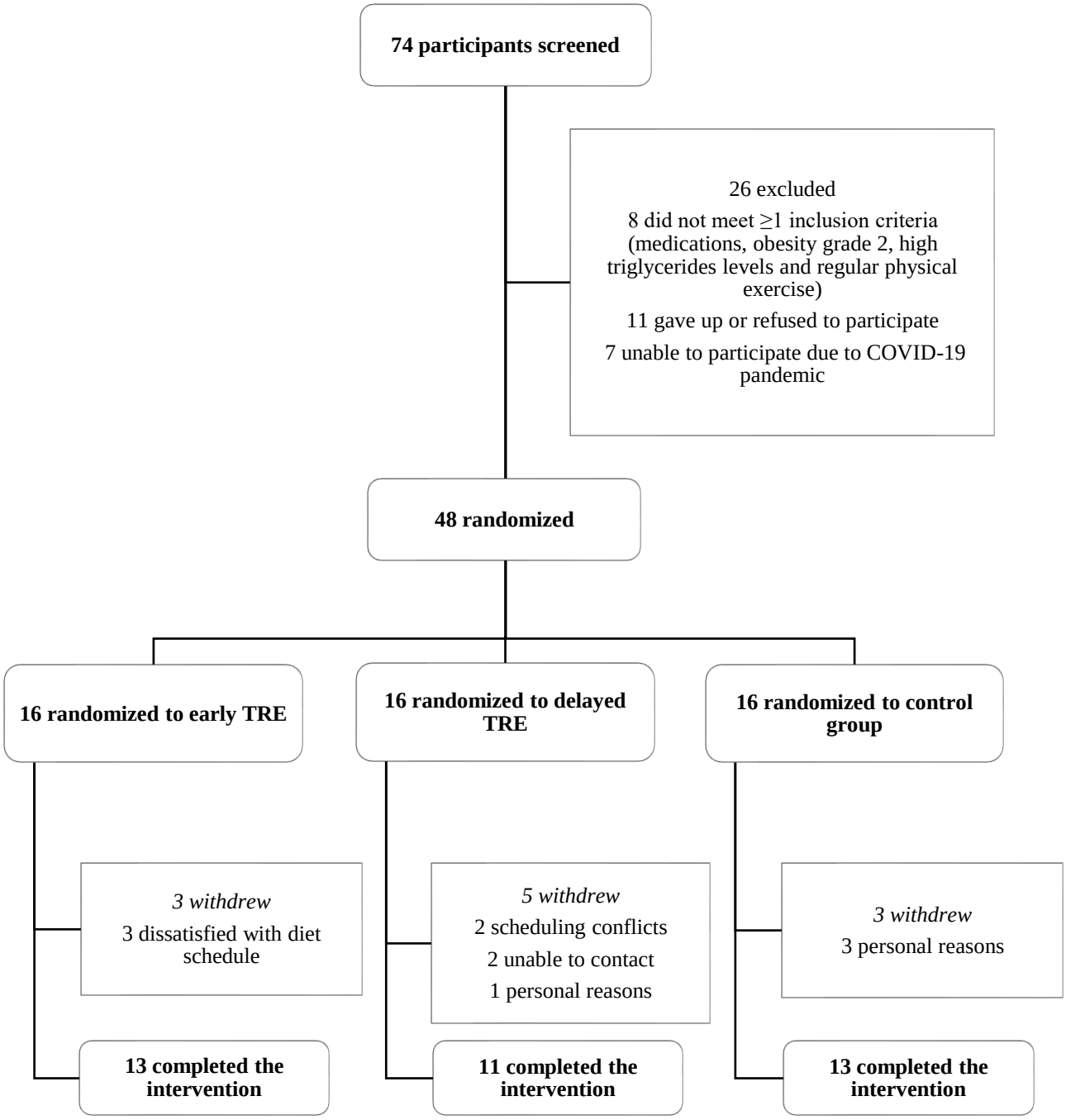
Figure 1. Participants flow through the trial.



TRE: time-restricted eating.

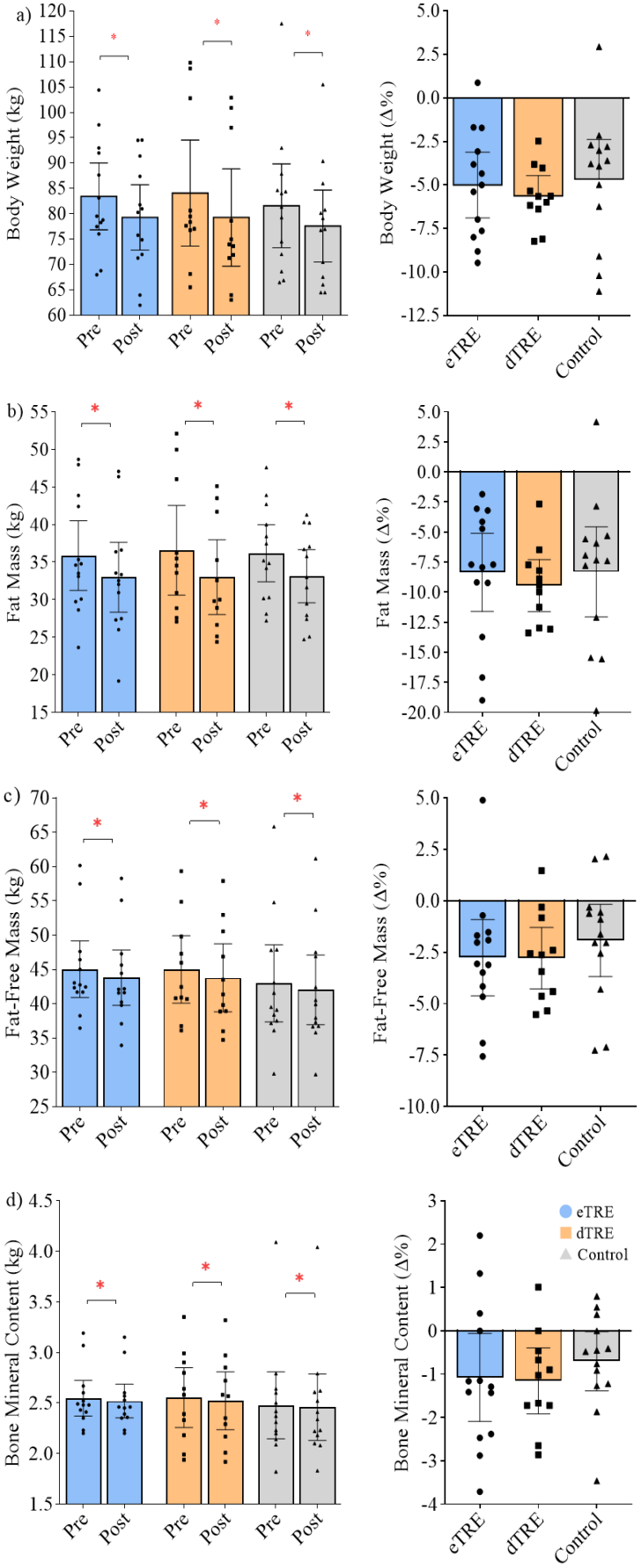


Figure 2. Data are presented as mean and 95% CI for absolute values before and after intervention (left) and their respective changes (%) (right). a) Body Weight; b) Fat Mass; c) Fat-free Mass; d) Bone Mineral Content. Blue, eTRE; orange, dTRE; and gray, control. The symbols represent the individuals in their groups. No significant group*time interactions were observed. *p <.05 for time main effect. TRE: time-restricted eating.

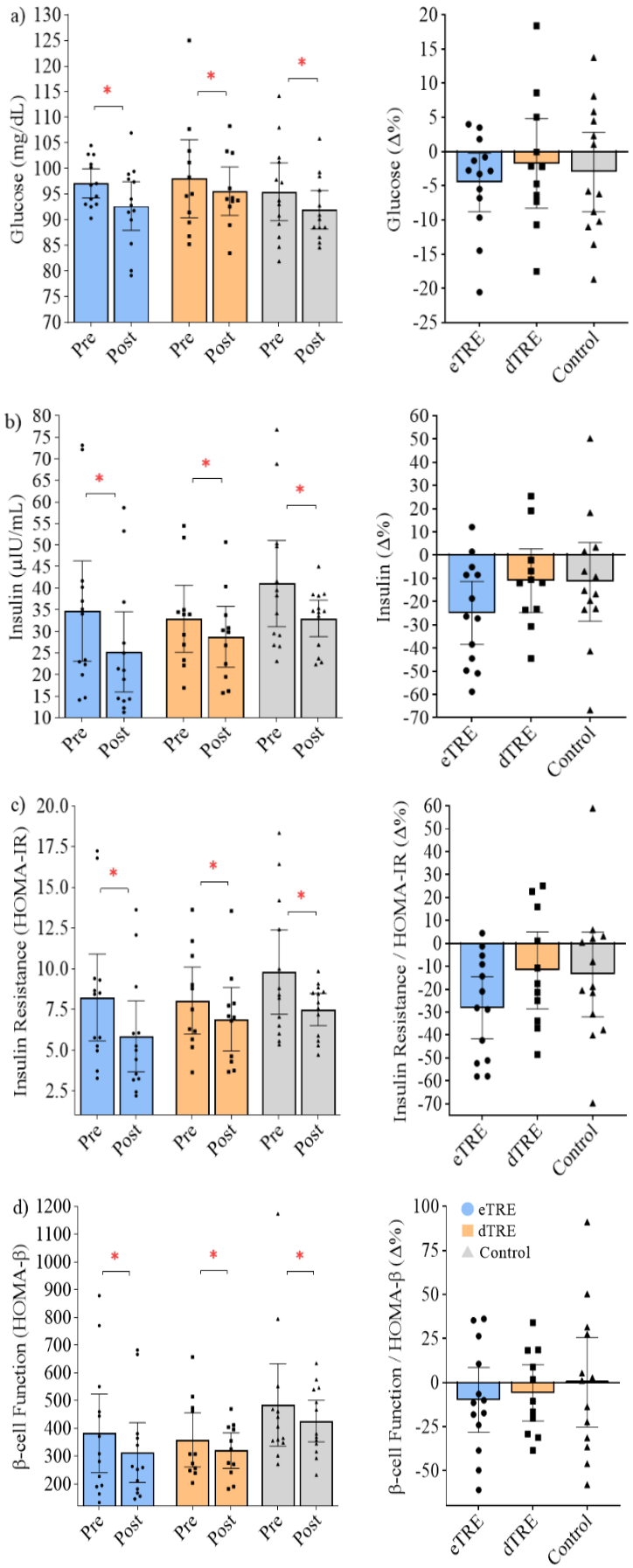


Figure 3. Data are presented as mean and 95% CI for absolute values before and after intervention (left) and their respective changes (%) (right). a) Fasting Glucose; b) Fasting Insulin; c) Insulin Resistance; d) β-cell Function. Blue, early TRE; orange, delayed TRE; and gray, control. The symbols represent the individuals in their groups. No significant time*group interactions were observed. *p <.05 for time main effect. TRE: time-restricted eating.

Table 1. Baseline Characteristics of the Study Participants[a].

	Early TRE (n = 16)	**Delayed TRE (n = 16)**	**Control (n = 16)**	**Randomized (n = 48)**	**Completed (n = 37)**	**Dropouts (n = 11)**
Age, mean (SD), Years	32 (5)	30 (6)	26 (4)	29 (6)	30 (6)	28 (4)
Sex						
Female, n (%)	14 (87.5)	14 (87.5)	14 (87.5)	42 (87.5)	31 (84)	11 (100)
Male, n (%)	2 (12.5)	2 (12.5)	2 (12.5)	6 (12.5)	6 (16)	0 (0)
Education levels						
Incomplete High School, n (%)	0 (0)	1 (6)	0 (0)	1 (2)	0 (0)	1 (9)
Complete High School, n (%)	7 (44)	4 (25)	2 (12.5)	13 (27)	10 (27)	3 (27)
Higher Education (in-progress or complete), n (%)	9 (56)	11 (69)	14 (87.5)	34 (71)	27 (73)	7 (64)
Chronotype, n (%), Types[b]						
Definitely Morning	1 (7)	0 (0)	1 (6)	2 (4)	2 (6)	0 (0)
Moderately Morning	5 (33)	2 (13)	3 (19)	10 (22)	7 (19)	3 (30)
Neither / Indifferent	9 (60)	10 (67)	9 (56)	28 (61)	23 (64)	5 (50)
Moderately Evening	0 (0)	2 (13)	3 (19)	5 (11)	4 (11)	1 (10)
Definitely Evening	0 (0)	1 (7)	0 (0)	1 (2)	0 (0)	1 (10)
Usual Fasting Time, mean (SD), hours/day	11 (3)	11 (3)	11 (2)	11 (3)	11 (2)	10 (4)
Usual sleep duration, mean (SD), hours/day	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)	7 (1)
Night Eating Questionnaire, mean (SD), Score	17 (6)	16 (7)	16 (6)	16 (6)	17 (6)	15 (7)
Height, mean (SD), m	1.65 (0.06)	1.64 (0.08)	1.65 (0.09)	1.64 (0.07)	1.64 (0.08)	1.64 (0.05)
Weight, mean (SD), kg	84.9 (10.5)	83.9 (13.4)	83.0 (12.3)	83.9 (11.9)	82.9 (12.8)	87.4 (7.5)
BMI, mean (SD), kg/m²	31.2 (2.7)	31.2 (2.8)	30.5 (2.9)	31.0 (2.8)	30.5 (2.7)	32.6 (2.3)
SBP, mean (SD), mm Hg	109 (9)	115 (16)	108 (10)	111 (12)	111 (12)	110 (13)
DBP, mean (SD), mm Hg	76 (7)	81 (13)	77 (10)	78 (10)	77 (11)	80 (10)
MAP, mean (SD), mm Hg	87 (7)	92 (14)	88 (9)	89 (11)	89 (11)	90 (11)
Resting Heart Rate, mean (SD), beats/min	72 (9)	73 (11)	73 (10)	72 (10)	72 (11)	74 (7)
Fasting Glucose, mg/dL[c]	99 (6)	99 (10)	96 (8)	98 (8)	98 (8)	96 (7)
Fasting Triglycerides, mg/dL[c]	94 (39)	95 (32)	99 (44)	96 (38)	95 (33)	98 (50)

Abbreviations: BMI, Body Mass Index (calculated as weight in kilograms divided by height in meters squared); DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure (calculated as DBP in millimeters of mercury multiplied by two plus systolic blood pressure in millimeters of mercury, and the result divided by three); SBP, Systolic Blood Pressure; TRE, Time-Restricted Eating; SI conversion factors: to convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113.

[a]Data are presented as mean (standard deviation; SD), unless otherwise indicated.
[b]Missing data (eTRE, n=15; dTRE, n=15; control, n=16; all participants: n=46; participants who completed the study: n=36).
[c]Missing data due to errors in blood collection (eTRE, n=15; dTRE; n =15; control, n=14; all participants: n=44; participants who completed the study: n=33).

Table 2. Comparison of pre- and post-intervention outcomes (per protocol analysis)[a]

Outcome Variable	Early TRE (n = 13)		Δ eTRE	Delayed TRE (n = 11)		Δ dTRE	Control Group (n = 13)		Δ CG	*Time p value*	*Group p value*	*Time*Group p value*
	Pre	**Post**		**Pre**	**Post**		**Pre**	**Post**				
BODY COMPOSITION												
Body Mass, Kg												
Total	83.46 (77.77 to 89.16)	79.31 (73.73 to 84.89)	-4.15 (-5.57 to -2.73)	84.12 (75.36 to 92.88)	79.32 (71.29 to 87.35)	-4.80 (-5.90 to -3.70)	81.62 (74.49 to 88.75)	77.62 (71.48 to 83.76)	-4.00 (-5.90 to -2.10)	0.000	0.901	0.679
Arms	8.85 (8.08 to 9.63)	8.45 (7.74 to 9.15)	-0.40 (-0.66 to -0.16)	9.13 (7.99 to 10.26)	8.80 (7.81 to 9.79)	-0.33 (-0.58 to -0.07)	9.15 (8.03 to 10.26)	8.68 (7.66 to 9.71)	-0.47 (-0.73 to -0.19)	0.000	0.861	0.770
Legs	30.01 (27.36 to 32.65)	28.72 (26.22 to 31.22)	-1.29 (-2.63 to 0.64)	29.24 (25.77 to 32.71)	27.81 (24.78 to 30.84)	-1.43 (-2.07 to -0.79)	29.82 (26.87 to 32.76)	28.34 (25.82 to 30.86)	-1.48 (-2.32 to -0.63)	0.000	0.921	0.972
Trunk	39.92 (36.68 to 43.17)	37.50 (34.55 to 40.45)	-2.42 (-3.62 to -1.23)	40.79 (35.93 to 45.65)	37.88 (33.38 to 42.38)	-2.91 (-3.61 to -2.21)	38.16 (34.78 to 41.54)	36.10 (33.19 to 39.01)	-2.06 (-3.09 to -1.03)	0.000	0.674	0.389
Fat Mass, Kg												
Total	35.89 (31.88 to 39.89)	32.99 (28.97 to 37.01)	-2.90 (-3,92 to -1.87)	36.59 (31.59 to 41.59)	33.01 (28.83 to 37.19)	-3.58 (-4.63 to -2.52)	36.17 (32.88 to 39.47)	33.13 (30.06 to 36.21)	-3.04 (-4.30 to -1.79)	0.000	0.993	0.641
Arms	3.66 (3.30 to 4.01)	3.40 (3.09 to 3.71)	-0.26 (-0.41 to -0.11)	3.77 (3.27 to 4.26)	3.60 (3.18 to 4.02)	-0.17 (-0.32 to -0.01)	3.94 (3.55 to 4.34)	3.65 (3.25 to 4.05)	-0.29 (-0.45 to -0.14)	0.000	0.576	0.516
Legs	13.42 (11.91 to 14.94)	12.50 (10.96 to 14.03)	-0.92 (-1.74 to -0.11)	12.64 (10.67 to 14.61)	11.57 (9.96 to 13.18)	-1.07 (-1.50 to -0.64)	13.15 (11.78 to 14.52)	12.08 (10.86 to 13.31)	-1.07 (-1.62 to -0.52)	0.000	0.769	0.951
Trunk	17.86 (15.11 to 20.61)	16.17 (13.67 to 18.66)	-1.69 (-2.47 to -0.92)	19.17 (15.97 to 22.37)	16.88 (14.17 to 19.59)	-2.29 (-2.96 to -1.63)	18.12 (16.06 to 20.18)	16.46 (14.52 to 18.41)	-1.66 (-2.37 to -0.94)	0.000	0.874	0.351
Fat-Free Mass, Kg												

Total	45.04 (41.48 to 48.60)	43.80 (40.30 to 47.30)	-1.24 (-1.94 to -0.55)	45.00 (40.87 to 49.13)	43.78 (39.60 to 47.96)	-1.22 (-1.76 to -0.68)	42.98 (38.11 to 47.85)	42.03 (37.64 to 46.42)	-0.95 (-1.73 to -0.18)	0.000	0.784	0.828
Arms	4.90 (4.25 to 5.56)	4.75 (4.16 to 5.33)	-0.15 (-0.28 to -0.03)	5.05 (4.29 to 5.82)	4.88 (4.17 to 5.59)	-0.17 (-0.28 to -0.07)	4.89 (3.97 to 5.81)	4.73 (3.86 to 5.59)	-0.16 (-0.29 to -0.04)	0.000	0.949	0.968
Legs	15.71 (14.20 to 17.22)	15.33 (13.94 to 16.73)	-0.38 (-0.94 to 0.20)	15.75 (13.97 to 17.54)	15.38 (13.64 to 17.12)	-0.37 (-0.66 to -0.08)	15.75 (13.74 to 17.77)	15.36 (13.52 to 17.20)	-0.39 (-0.71 to -0.07)	0.002	0.999	0.994
Trunk	21.16 (19.70 to 22.62)	20.54 (18.95 to 22.14)	-0.62 (-1.25 to 0.02)	20.83 (19.00 to 22.67)	20.26 (18.39 to 22.12)	-0.57 (-1.09 to -0.07)	19.28 (17.44 to 21.12)	18.88 (17.22 to 20.54)	-0.40 (-0.88 to 0.08)	0.001	0.291	0.826
Bone Mineral Content, Kg												
Total	2.55 (2.39 to 2.70)	2.52 (2.38 to 2.66)	-0.03 (-0.05 to -0.01)	2.55 (2.31 to 2.80)	2.52 (2.28 to 2.76)	-0.03 (-0.05 to -0.02)	2.48 (2.19 to 2.76)	2.46 (2.18 to 2.74)	-0.02 (-0.03 to -0.00)	0.000	0.918	0.324
Arms	0.30 (0.27 to 0.33)	0.30 (0.27 to 0.33)	0.00 (-0.01 to 0.00)	0.30 (0.27 to 0.34)	0.31 (0.28 to 0.34	0.01 (-0.00 to 0.01)	0.31 (0.26 to 0.36)	0.31 (0.27 to 0.36)	0.00 (-0.01 to 0.01)	0.985	0.869	0.378
Legs	0.88 (0.79 to 0.97)	0.88 (0.80 to 0.97)	0.00 (-0.01 to 0.02)	0.86 (0.77 to 0.95)	0.86 (0.77 to 0.95)	0.00 (-0.00 to 0.01)	0.90 (0.76 to 1.04)	0.90 (0.77 to 1.03)	0.00 (-0.01 to 0.01)	0.412	0.864	0.955
Trunk	0.82 (0.77 to 0.88)	0.80 (0.75 to 0.85)	-0.02 (-0.04 to -0.01)	0.79 (0.70 to 0.88)	0.75 (0.67 to 0.84)	-0.04 (-0.05 to -0.02)	0.77 (0.68 to 0.85)	0.75 (0.66 to 0.84)	-0.02 (-0.03 to 0.00)	0.000	0.549	0.156
Body Fat, %												
Total	42.81 (39.79 to 45.83)	41.35 (38.09 to 44.62)	-1.46 (-2.16 to -0.74)	43.18 (41.05 to 45.31)	41.42 (39.41 to 43.42)	-1.76 (-2.41 to -1,12)	44.51 (41.74 to 47.27)	42.83 (39.84 to 45.83)	-1.68 (-2.36 to -0.99)	0.000	0.696	0.812
Arms	41.69 (38.10 to 45.29)	40.63 (37.21 to 44.06)	-1.06 (-1.82 to -0.31)	41.54 (38.23 to 44.84)	41.27 (37.86 to 44.68)	-0.27 (-1.03 to 0.50)	44.06 (39.78 to 48.34)	42.86 (38.38 to 47.34)	-1.20 (-1.90 to -0.50)	0.000	0.691	0.172
Legs	44.64 (42.07 to 47.21)	43.29 (40.47 to 46.12)	-1.35 (-2.05 to -0.65)	42.86 (39.74 to 45.99)	41.40 (38.29 to 44.51)	-1.46 (-1.92 to -1.00)	44.38 (41.06 to 47.70)	42.89 (39.51 to 46.28)	-1.49 (-2.14 to -0.83)	0.000	0.664	0.953

Trunk	44.16 (40.39 to 47.93)	42.56 (38.54 to 46.58)	-1.60 (-2.67 to -0.53)	46.35 (43.68 to 49.01)	43.99 (41.72 to 46.26)	-2.36 (-3.33 to -1.38)	47.34 (44.65 to 50.02)	45.40 (42.22 to 48.58)	-1.94 (-2.97 to -0.91)	0.000	0.473	0.589
Body Mass Index, kg/m²	30.78 (29.35 to 32.21)	29.26 (27.72 to 30.79)	-1.52 (-2.02 to - 1.03)	30.54 (28.94 to 32.14)	28.82 (27.33 to 30.31)	-1.72 (-2.06 to -1,39)	30.08 (28.48 to 31.69)	28.66 (27.15 to 30.17)	-1.42 (-2.05 to -0.80)	0.000	0.835	0.643
CARDIOMETABOLIC PARAMETERS AND ENERGY METABOLISM												
Glucose, mg/dL	97.15 (94.73 to 99.58)	92.74 (88.64 to 96.85)	-4.41 (-8.06 to -0.76)	98.05 (91.67 to 104.44)	95.63 (91.70 to 99.57)	-2.42 (-8.13 to 3.29)	95.48 (90.61 to 100.35)	92.01 (88.75 to 95.28)	-3.47 (-8.50 to 1.56)	0.017	0.549	0.841
Mean Glucose, mg/dL/120 min[b]	123.20 (111.78 to 134.61)	114.98 (101.21 to 128.75)	-8.22 (-19.95 to 3.51)	118.30 (110.44 to 126.16)	121.77 (109.15 to 134.39)	3.47 (-7.75 to 14.69)	119.15 (109.84 to 128.47)	109.95 (100.85 to 119.05)	-9.20 (-16.22 to -2.18)	0.122	0.655	0.160
Insulin, µIU/mL	34.67 (24.64 to 44.71)	25.27 (17.23 to 33.30)	-9.40 (-13.74 to -5.07)	32.91 (26.38 to 39.45)	28.76 (22.83 to 34.69)	-4.15 (-8.83 to 0.53)	41.10 (32.47 to 49.74)	33.01 (29.35 to 36.66)	-8.09 (-16.09 to -0.10)	0.000	0.206	0.264
HOMA-IR	8.24 (5.93 to 10.54)	5.84 (3.96 to 7.72)	-2.40 (-3.40 to -1.39)	8.03 (6.31 to 9.76)	6.89 (5.25 to 8.52)	-1.14 (-2.59 to 0.30)	9.79 (7.56 to 12.02)	7.50 (6.64 to 8.35)	-2.29 (-4.42 to -0.16)	0.000	0.328	0.366
HOMA-β	382.40 (260.16 to 504.64)	312.85 (219.94 to 405.76)	-69.55 (-124.71 to -14.39)	358.40 (276.66 to 440.15)	319.84 (265.98 to 373.71)	-38.56 (-96.00 to 18.88)	484.06 (355.34 to 612.79)	426.76 (362.17 to 491.35)	-57.3 (-171.93 to 57.33)	0.020	0.082	0.747
Quicki Index	0.29 (0.28 to 0.30)	0.30 (0.29 to 0.32)	0.01 (0.01 to 0.02)	0.29 (0.28 to 0.30)	0.29 (0.29 to 0.30)	0.00 (0.00 to 0.01)	0.28 (0.27 to 0.29)	0.29 (0.28 to 0.29)	0.01 (0.00 to 0.01)	0.000	0.085	0.148
Matsuda Index[c]	2.86 (1.91 to 3.80)	3.61 (2.38 to 4.84)	0.75 (0.20 to 1.31)	2.37 (1.90 to 2.85)	2.45 (1.83 to 3.08)	0.08 (-0.25 to 0.41)	2.22 (1.27 to 3.17)	2.38 (1.73 to 3.03)	0.16 (-0.71 to 1.03)	0.071	0.322	0.118
Cholesterol, mg/dL												
Total	179.44 (157.98 to 200.90)	166.69 (145.77 to 187.60)	-12.75 (-23.00 to -2.50)	205.84 (180.53 to 231.16)	193.45 (178.76 to 208.15)	-12.39 (-31.80 to 7.03)	197.25 (170.56 to 223.93)	172.16 (153.96 to 190.36)	-25.09 (-45.05 to -5.12)	0.001	0.161	0.540
LDL	114.03 (90.42 to 137.64)	105.82 (83.66 to 127.99)	-8.21 (-16.15 to -0.26)	137.87 (115.70 to 160.04)	131.01 (116.68 to 145.33)	-6.86 (-21.77 to 8.04)	119.40 (95.14 to 143.67)	104.67 (88.98 to 120.37)	-14.73 (-30.13 to 0.67)	0.011	0.125	0.723

HDL	44.27 (39.60 to 48.94)	40.88 (36.91 to 44.85)	-3.39 (-6.49 to -0.29)	47.19 (41.09 to 53.29)	41.92 (36.95 to 46.89)	-5.27 (-9.73 to -0.81)	52.96 (45.28 to 60.64)	45.44 (38.80 to 52.07)	-7.52 (-11.39 to -3.66)	0.000	0.268	0.261
Non-HDL	135.16 (111.06 to 159.27)	125.80 (102.69 to 148.91)	-9.36 (-17.00 to -1.73)	158.65 (135.63 to 181.68)	151.54 (136.90 to 166.17)	-7.11 (-22.43 to 8.19)	144.29 (119.40 to 169.17)	126.72 (110.23 to 143.22)	-17.57 (-34.80 to -0.33)	0.006	0.176	0.637
Triglycerides, mg/dL	105.68 (72.33 to 139.03)	99.89 (65.90 to 133.88)	-5.79 (-14.77 to 3.18)	103.90 (90.65 to 117.16)	102.64 (85.53 to 119.76)	-1.26 (-15.14 to 12.63)	124.41 (94.46 to 154.36)	110.25 (76.68 to 143.82)	-14.16 (-33.38 to 5.06)	0.101	0.701	0.566
β-Hydroxybutyrate, mmol/L[d]	0.11 (0.08 to 0.14)	0.29 (0.10 to 0.48)	0.18 (0.00 to 0.37)	0.12 (0.07 to 0.17)	0.19 (0.12 to 0.26)	0.07 (0.01 to 0.13)	0.10 (0.05 to 0.15)	0.32 (0.16 to 0.48)	0.22 (0.05 to 0.39)	0.000	0.483	0.143
Resting Metabolic Rate, Kcal/Day	1712.07 (1577.05 to 1847.10)	1642.23 (1503.12 to 1781.35)	-69.84 (-149.13 to 9.45)	1832.28 (1625.87 to 2038.68)	1728.92 (1543.82 to 1914.02)	-103.36 (-167.35 to -39.37)	1792.39 (1633.85 to 1950.93)	1660.45 (1547.19 to 1773.71)	-131.94 (-236.89 to -26.99)	0.000	0.673	0.633
Resting Respiratory Exchange Ratio	0.77 (0.73 to 0.81)	0.74 (0.71 to 0.77)	-0.03 (-0.07 to 0.07)	0.76 (0.72 to 0.79)	0.74 (0.69 to 0.79)	-0.02 (-0.05 to 0.02)	0.76 (0.71 to 0.80)	0.73 (0.69 to 0.78)	-0.03 (-0.07 to 0.02)	0.047	0.910	0.889
Peak Oxygen Consumption, mL/kg/min[e]	25.78 (23.13 to 28.43)	25.93 (22.16 to 29.71)	0.15 (-2.55 to 2.86)	24.41 (21.94 to 26.89)	24.06 (22.00 to 26.12)	-0.35 (-1.99 to 1.28)	27.44 (25.34 to 29.55)	26.56 (24.19 to 28.93)	-0.88 (-2.78 to 1.01)	0.563	0.182	0.817
SUBJECTIVE APPETITE, SLEEP QUALITY, AND RISK OF BINGE EATING												
Hunger, scale 0-100 mm	53 (38 to 68)	43 (32 to 54)	-10 (-25 to 5)	48 (34 to 62)	35 (22 to 49)	-13 (-31 to 5)	58 (47 to 70)	65 (56 to 75)	7 (-6 to 20)	0.254	0.009	0.127
Satiety, scale 0-100 mm	48 (34 to 63)	61 (51 to 72)	13 (-5 to 31)	46 (33 to 60)	62 (46 to 78)	16 (-2 to 33)	40 (28 to 52)	39 (31 to 48)	-1 (-7 to 6)	0.037	0.050	0.116
Desire to eat, scale 0-100 mm	61 (47 to 74)	43 (29 to 57)	-18 (-37 to 1)	52 (37 to 67)	33 (21 to 45)	-19 (-36 to -2)	63 (49 to 77)	68 (57 to 80)	5 (-7 to 18)	0.030	0.013	0.031
Capacity to eat, scale 0-100 mm	65 (52 to 79)	54 (42 to 65)	-11 (-30 to 7)	59 (44 to 74)	45 (32 to 57)	-14 (-29 to 0.2)	71 (60 to 81)	73 (60 to 86)	2 (-9 to 13)	0.078	0.036	0.155
Binge Eating Disorder, score	16 (12 to 20)	6 (4 to 9)	-10 (-13 to -6)	12 (7 to 17)	7 (4 to 10)	-5 (-8 to -2)	14 (12 to 16)	8 (5 to 10)	-6 (-9 to -4)	0.000	0.746	0.219
Sleep Quality Index[f]	8 (6 to 10)	5 (4 to 6)	-3 (-5 to -2)	8 (6 to 11)	5 (4 to 7)	-3 (-4 to -1)	8 (6 to 9)	5 (3 to 6)	-3 (-4 to -1)	0.000	0.890	0.819

Abbreviations: HDL, high-density lipoprotein; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; TRE, time-restricted eating; QUICKI, quantitative insulin sensitivity check index.

SI conversion factors: To convert total, HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert insulin to picomoles per liter, multiply by 6.945.

[a]Data are presented as mean (95% confidence interval, CI). Data analyzed only for completers (eTRE n=13; dTRE n=11; CG n=13).
[b]Variable with missing data due to errors in the collection instruments (eTRE n=13; dTRE n=10; CG n=13). One individual in the dTRE group was excluded from the analysis due to insufficient data in the OGTT after 8 weeks.
[c]Variable with missing data due to errors in the collection instruments (eTRE n=10; dTRE n=9; CG n=11). Seven participants (eTRE: 3; dTRE: 2; control: 2) were excluded from the analysis due to missing data at point 120 min.
[d]Variable with missing data due to errors in the collection instruments (eTRE n=12; dTRE n=9; CG n=10).
[e]Variable with missing data due to errors in the collection instruments (eTRE n=12; dTRE n=11; CG n=12.
[f]Variable with missing data due to errors in the collection instruments (eTRE n=13; dTRE n=10; CG n=12).

Supplementary Online Content

eMethods

Eligibility Criteria

Participants met the following inclusion criteria: females and males between 20 and 40 years, body mass index between 25.0 and 34.9 kg/m^2, and not engaging in any structured exercise program during the past three months. Participants were free of cardiovascular disease, type 1 or 2 diabetes mellitus, hypertension, and dyslipidemia. Current cigarette smoking, use of supplements or medications that could affect the main outcomes of the study, unstable weight for three months before the beginning of the study (defined as ≥ 5% weight loss or gain), regular alcohol consumption (2 servings/day for males and 1 serving/day for females) and regular fasting (> 16 h per day) were also exclusion criteria for the present study. Moreover, were excluded individuals with night eating syndrome, night shift workers, and pregnant, lactating, or menopausal women, as well as those with fasting plasma glucose and triglyceride levels > 126 mg/dL and > 150 mg/dL, respectively.

Dietary Interventions

Daily, the participants sent to a nutritionist researcher, through a smartphone messenger app, photos of the three meals immediately before consuming them. Participants were strongly encouraged to eat only the meals prescribed by the nutritionist and to eat at the times indicated. The eating schedules were modestly customized by allowing each participant could advance or delay the intake of the first meal by a maximum of one hour. Nevertheless, the time of the last meal was adjusted according to the time of the first meal. For example, if the first meal was eaten at 07:00, the last meal would be at 15:00 in the eTRE group and at 19:00 in the control group. On the day before the final assessment, individuals in the eTRE group were instructed to consume the last meal at ~20:00 to standardize the length of the fast relative to the other groups. Thus, all participants were assessed after the same duration of fasting.

Measures

Body Composition

Participants were instructed to empty their bladder and to remove any metal accessories before this assessment. They were positioned in dorsal decubitus (supine), aligned, and centered on the scanning table with hips and shoulders extended and hands in a neutral position. Participants were evaluated pre-and post-intervention at the same time of day and in the same nutritional state (fasted) at each assessment. The equipment was calibrated before evaluations according to the manufacturer's specifications.

Resting Metabolic Rate and Respiratory Exchange Ratio

Resting metabolic rate and respiratory exchange ratio were assessed in an open-circuit calorimeter (Quark RMR, Cosmed) calibrated at the beginning of the day, using the canopy dilution technique. Resting metabolic rate assessments were performed between 6:30 and 8:30 in a room with controlled temperature, sound, and light. Participants were positioned in a supine position for approximately 30 minutes, and the first 10 minutes of gas collection were excluded from the analysis. Thus, mean VO2 and VCO2 (L / min) values obtained during the final 20 minutes were used to calculate resting metabolic rate for a 24-h period, according to the Weir equation[1].The respiratory exchange ratio was determined by VCO2 / VO2. Participants were instructed to avoid moderate-to-high intensity physical activities and not consume alcohol, caffeine, or yerba mate (*Ilex paraguariensis*) during the 24 hours preceding the test. They could intake only water ad libitum. Also, participants were instructed to sleep for at least eight hours and to fast for 11 hours prior to assessments. Finally, participants were instructed to be transported to the laboratory in a motorized vehicle, if possible.

Blood Collection and Analysis

Blood (~10 mL) was collected in EDTA vacuum tubes and centrifuged for 10 minutes at 1000 g and 4°C. Plasma was immediately stored at -80°C for later analyses. All blood samples were analyzed in singlicate. Glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured by colorimetric method on an automatic analyzer (Cobas C111, Roche). Low-density lipoprotein cholesterol was determined using the Friedewald equation[2]. Non-high-density lipoprotein cholesterol was calculated as total cholesterol minus high-density lipoprotein cholesterol[3]. Capillary blood β-hydroxybutyrate levels were analyzed in fasting using a ketone monitor (FreeStyle Optium, Abbot). Insulin levels were assayed using an enzyme-linked immunosorbent assay kit (DRG International, Inc.) according to the manufacturers' instructions. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin × fasting glucose / 405, where the unit of measure for insulin is in micro-international units per milliliter (μIU/mL) and the unit of measure for glucose is milligrams per deciliter (mg/dL)[4]. The homeostasis model assessment of β-cells functional capacity (HOMA-β) was calculated as fasting insulin (μIU/mL) x 20 / (fasting glucose [mg/dL] x

0.0555) - 3.5[4]. The quantitative insulin sensitivity check index (QUICKI) was derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose: 1 / (log(fasting insulin μIU/mL) + log(fasting glucose mg/dL))[5]. For the 2-hour oral glucose tolerance test, participants consumed 75 g loads of dextrose (Max Titanium®) diluted in 300 mL of water within 5 minutes. Then, blood (~5 mL) was subsequently collected at 30, 60, 90, and 120 minutes. Plasma glucose levels were analyzed at all points, while insulin levels were measured only in fasting and 120 minutes after glucose intake. The Matsuda Index was calculated as 10.000 divided by square root of plasma glucose and insulin concentrations at times 0 and 120 min (glucose 0 [mg/dL] x glucose 120 [mg/dL] x insulin 0 [μIU/mL] x insulin 120 [μIU/mL]) from OGTT[6,7].

Subjective Appetite, Binge Eating Risk, Sleep Quality and Chronotype

Participants rated their appetite levels, based on how they were currently feeling, across four dimensions (hunger, satiety, desire to eat, and capacity to eat) using an adapted Visual Analog Scale[8]. The scale range is 0-100 mm, and each end represents the extremes. The scale was administered before the standard meal pre- and post-8 weeks. Binge eating risk was analyzed by the Binge Eating Scale, a 16-item self-report questionnaire. Participants' scores can range from 0 to 46, with higher scores indicating more severe binge eating problems. The clinical cutoff scores for this scale representing low (<17), moderate (18–26), and high (>27) binge eating risks[9]. The Pittsburgh Sleep Quality Index[10] was used to analyze the sleep quality through 19 self-rated questions about seven sleep components. The score can range from 0 to 3 for each component, with a maximum score of 21 points. Scores above 5 points indicate poor quality of sleep. The Morningness-Eveningness Questionnaire was used only at the beginning of the study to determine the chronotype of participants. The score on this questionnaire can range from 16 to 86, with a higher score indicating a stronger morningness preference. For the global score assessment, each item is totaled. The sum is converted to a 5-point scale: definitely morning type (70–86), moderately morning type (59–69), neither type (42–58), moderately evening type (31–41), and definitely evening type (16–30)[11]. Except for the Binge Eating Scale, which was completed in the laboratory, the other questionnaires were answered online using a Google Forms link.

Maximum Effort Exercise Test

The maximum effort exercise test was conducted on a cycle ergometer (Ergo-fit Cycle 167 med). During the test, respiratory gas analysis was performed breath-by-breath using an open-circuit spirometry system (Quark CPET, Cosmed). The test started with a warm-up, which consisted of cycling for 3 min at 20 watts, followed by increments of 20 watts every 1 min until exhaustion. During the test, pedaling cadence was required to be at least 60 revolutions per minute. Following completion of the test, there was a recovery period of 3 min at 20 watts. Heart rate was measured continuously using chest belt telemetry (Polar Electro Oy), and the volunteers were verbally encouraged to perform maximum effort during the test. The following criteria were adopted to indicate exhaustion, with two or more items required to end the exercise test: volitional fatigue, respiratory exchange ratio ≥ 1.15, heart rate ≥ 95% of age-predicted maximum heart rate (220−age), pedaling cadence < 60 revolutions per minute, or tendency to a plateau in the oxygen consumption (VO_2) with increasing load. The VO_2 peak value was considered the highest VO_2 value attained during the final test[12].

Physical Activity Levels

Participants' physical activity levels were evaluated in two ways. The International Physical Activity Questionnaire-Short Form (IPAQ-SF)[13] was completed four times during the study (pre-intervention and after one, four, and eight weeks). The IPAQ-SF questionnaire was completed online through a Google Forms link sent to the participants. Data were analyzed as metabolic equivalent of task / min / week. Additionally, participants installed the Google Fit app to measure their physical activity levels. At the end of the first, fourth, and eighth week of study, participants reported their "move minutes per week" provided by the app.

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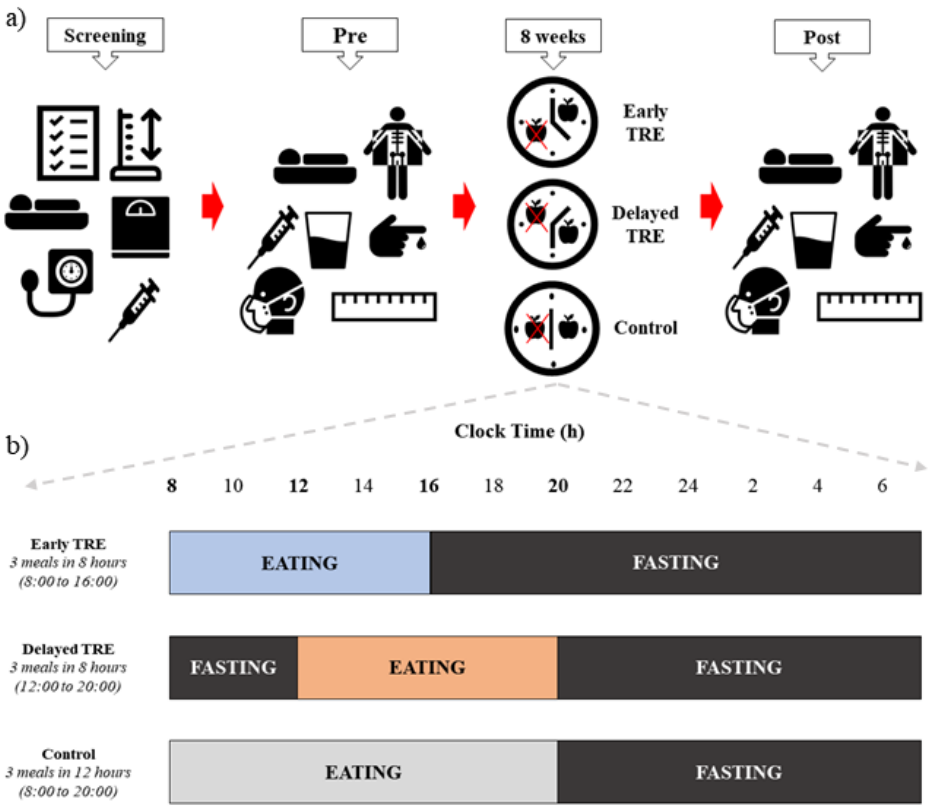
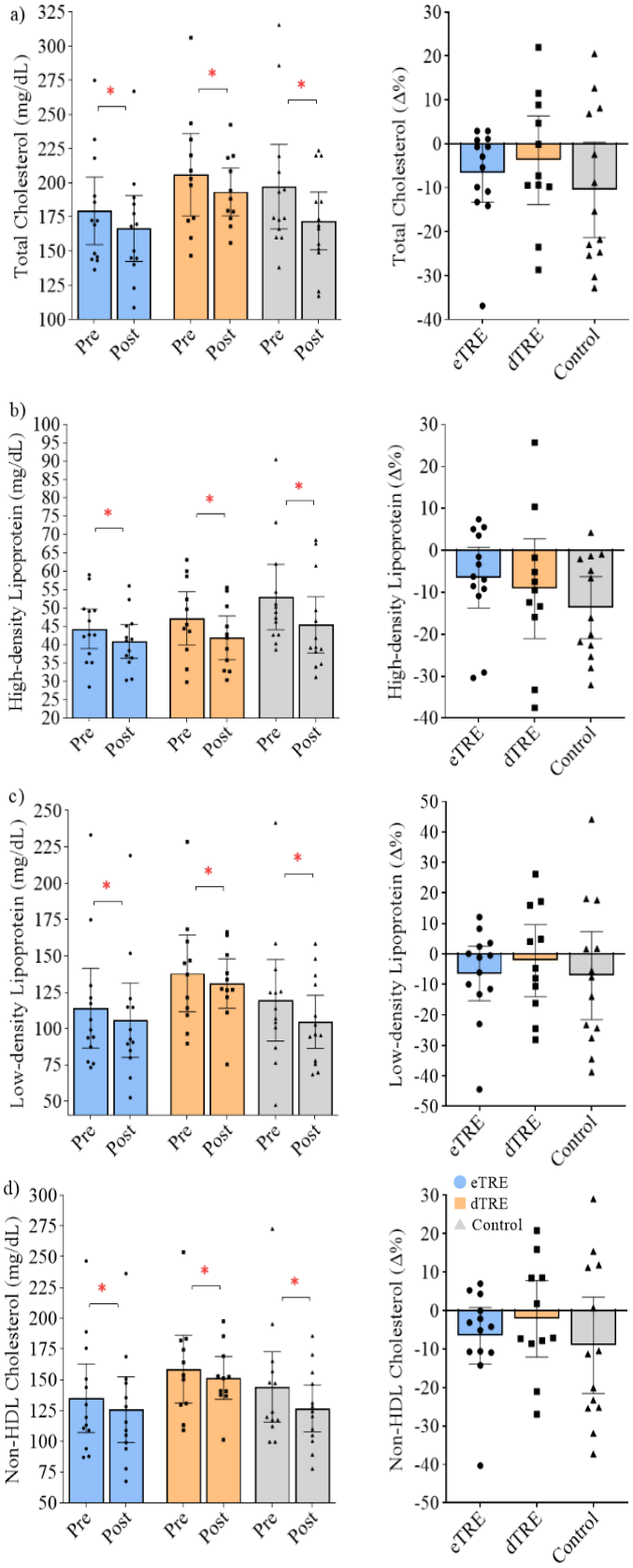
eFigure 1. Study Protocol



a) Experimental Design. Assessments performed at screening after signing the consent form: body weight, height, body mass index, resting metabolic rate, blood pressure, and initial blood collection. Assessments performed before and after 8 weeks: body weight, resting metabolic rate, body composition, collection of venous and capillary blood, 2-h -hour oral glucose tolerance test, questionnaires, and maximal effort test. b) Dietary Interventions. The eTRE and dTRE groups consumed their 3 daily meals, respectively, between 8:00 and 16:00 and between 12:00 and 20:00, totaling 16 hours of fasting per 24-hour period. TRE: time-restricted eating.

eFigure 2. Lipid Profile



Data are presented as mean and 95% CI for absolute values before and after intervention (left) and for their respective changes (%) (right). a) Fasting Total Cholesterol; b) Fasting High-density Lipoprotein Cholesterol c) Fasting Low-density Lipoprotein Cholesterol; d) Fasting Non-High-density Lipoprotein Cholesterol. Blue, eTRE; orange, dTRE; and gray, control. The symbols represent the individuals in their groups. No significant time*group interactions were observed. *p <.05 for time main effect. TRE: time-restricted eating.

eTable 1. Comparison of pre- and post-intervention outcomes (intention-to-treat analysis)[a]

Outcome Variable	Early TRE (n = 16)		Δ eTRE	Delayed TRE (n = 16)		Δ dTRE	Control Group (n = 16)		Δ CG	*Time p value*	*Group p value*	*Time*Group p value*
	Pre	Post		Pre	Post		Pre	Post				
BODY COMPOSITION												
Body Mass, Kg												
Total	85.02 (79.91 to 90.12)	80.86 (75.83 to 85.90)	-4.16 (-5.57 to -2.73)	83.75 (77.06 to 90.44)	78.95 (72.94 to 84.95)	-4.80 (-5.90 to -3.70)	83.10 (76.63 to 89.57)	79.10 (73.53 to 84.67)	-4.00 (-5.90 to -2.10)	0.000	0.877	0.679
Arms	9.00 (8.32 to 9.68)	8.59 (7.98 to 9.21)	-0.41 (-0.66 to -0.16)	9.12 (8.26 to 9.98)	8.79 (8.07 to 9.52)	-0.33 (-0.58 to -0.07)	9.34 (8.34 to 10.34)	8.88 (7.96 to 9.80)	-0.46 (-0.73 to -0.19)	0.000	0.858	0.770
Legs	30.53 (28.27 to 32.79)	29.25 (27.05 to 31.44)	-1.28 (-2.63 to 0.06)	29.23 (26.42 to 32.05)	27.81 (25.37 to 30.24)	-1.42 (-2.07 to -0.79)	30.03 (27.45 to 32.61)	28.55 (26.37 to 30.73)	-1.48 (-2.32 to -0.63)	0.000	0.727	0.972
Trunk	40.75 (37.85 to 43.65)	38.33 (35.64 to 41.01)	-2.42 (-3.62 to -1.23)	40.58 (36.82 to 44.34)	37.67 (34.24 to 41.10)	-2.91 (-3.61 to -2.21)	39.12 (35.93 to 42.31)	37.06 (34.28 to 39.84)	-2.06 (-3.09 to -1.03)	0.000	0.773	0.389
Fat Mass, Kg												
Total	36.97 (33.41 to 40.54)	34.08 (30.48 to 37.68)	-2.89 (-3.92 to -1.87)	37.10 (33.25 to 40.94)	33.52 (30.43 to 36.61)	-3.58 (-4.63 to -2.52)	36.79 (33.81 to 39.76)	33.75 (30.95 to 36.55)	-3.04 (-4.30 to -1.79)	0.000	0.993	0.641
Arms	3.76 (3.43 to 4.08)	3.50 (3.21 to 3.79)	-0.26 (-0.41 to -0.11)	3.89 (3.49 to 4.30)	3.73 (3.38 to 4.07)	-0.16 (-0.32 to -0.01)	4.06 (3.68 to 4.44)	3.76 (3.38 to 4.15)	-0.30 (-0.45 to -0.14)	0.000	0.489	0.516
Legs	13.62 (12.35 to 14.90)	12.70 (11.36 to 14.04)	-0.92 (-1.74 to -0.11)	13.06 (11.39 to 14.72)	11.99 (10.62 to 13.36)	-1.07 (-1.50 to -0.64)	13.09 (11.87 to 14.31)	12.02 (10.92 to 13.12)	-1.07 (-1.62 to -0.52)	0.000	0.734	0.951

Trunk	18.63 (16.19 to 21.08)	16.94 (14.70 to 19.18)	-1.69 (-2.47 to -0.92)	19.16 (16.75 to 21.58)	16.87 (14.91 to 18.82)	-2.29 (-2.96 to -1.63)	18.65 (16.73 to 20.57)	17.00 (15.17 to 18.82)	-1.65 (-2.37 to -0.94)	0.000	0.988	0.351
Fat-Free Mass, Kg												
Total	45.49 (42.46 to 48.53)	44.25 (41.25 to 47.25)	-1.24 (-1.94 to -0.55)	44.17 (40.95 to 47.39)	42.95 (39.68 to 46.23)	-1.22 (-1.76 to -0.68)	43.79 (39.44 to 48.13)	42.84 (38.95 to 46.73)	-0.95 (-1.73 to -0.18)	0.000	0.778	0.828
Arms	4.95 (4.41 to 5.49)	4.80 (4.32 to 5.27)	-0.15 (-0.28 to -0.03)	4.93 (4.35 to 5.51)	4.75 (4.22 to 5.29)	-0.18 (-0.28 to -0.07)	4.97 (4.16 to 5.77)	4.81 (4.05 to 5.56)	-0.16 (-0.29 to -0.04)	0.000	0.994	0.968
Legs	16.02 (14.72 to 17.32)	15.65 (14.43 to 16.86)	-0.37 (-0.94 to 0.20)	15.34 (13.91 to 16.76)	14.97 (13.58 to 16.36)	-0.37 (-0.66 to -0.08)	16.01 (14.23 to 17.79)	15.62 (14.01 to 17.23)	-0.39 (-0.71 to -0.07)	0.002	0.743	0.994
Trunk	21.24 (19.95 to 22.52)	20.62 (19.18 to 22.06)	-0.62 (-1.25 to 0.02)	20.64 (19.15 to 22.13)	20.06 (18.52 to 21.60)	-0.58 (-1.09 to -0.07)	19.69 (17.99 to 21.38)	19.29 (17.75 to 20.83)	-0.40 (-0.88 to 0.08)	0.001	0.397	0.826
Bone Mineral Content, Kg												
Total	2.56 (2.43 to 2.69)	2.53 (2.41 to 2.66)	-0.03 (-0.05 to -0.01)	2.50 (2.31 to 2.69)	2.47 (2.28 to 2.65)	-0.03 (-0.05 to -0.02)	2.53 (2.27 to 2.80)	2.52 (2.25 to 2.78)	-0.01 (-0.03 to -0.00)	0.000	0.866	0.325
Arms	0.30 (0.28 to 0.32)	0.30 (0.27 to 0.32)	0.00 (-0.01 to 0.00)	0.30 (0.27 to 0.33)	0.30 (0.28 to 0.33)	0.00 (-0.00 to 0.01)	0.32 (0.27 to 0.36)	0.32 (0.27 to 0.36)	0.00 (-0.01 to 0.01)	0.985	0.775	0.378
Legs	0.88 (0.81 to 0.95)	0.88 (0.81 to 0.96)	0.00 (-0.01 to 0.02)	0.84 (0.77 to 0.91)	0.84 (0.78 to 0.91)	0.00 (-0.00 to 0.01)	0.91 (0.79 to 1.04)	0.91 (0.80 to 1.03)	0.00 (-0.01 to 0.01)	0.411	0.551	0.955
Trunk	0.82 (0.77 to 0.87)	0.80 (0.75 to 0.84)	-0.02 (-0.04 to -0.01)	0.78 (0.72 to 0.85)	0.75 (0.68 to 0.81)	-0.03 (-0.05 to -0.02)	0.78 (0.70 to 0.86)	0.77 (0.68 to 0.85)	-0.01 (-0.03 to 0.00)	0.000	0.528	0.156
Body Fat, %												
Total	43.28 (40.72 to 45.85)	41.83 (39.01 to 44.64)	-1.45 (-2.16 to -0.74)	44.03 (42.26 to 45.80)	42.27 (40.58 to 43.96)	-1.76 (-2.41 to -1.12)	44.43 (42.03 to 46.84)	42.76 (40.11 to 45.40)	-1.67 (-2.36 to -0.99)	0.000	0.856	0.812

Arms	42.02 (39.08 to 44.96)	40.96 (38.16 to 43.75)	-1.06 (-1.82 to -0.31)	42.85 (40.13 to 45.58)	42.59 (39.75 to 45.43)	-0.26 (-1.03 to 0.50)	44.21 (40.46 to 47.95)	43.01 (39.05 to 46.96)	-1.20 (-1.90 to -0.50)	0.000	0.662	0.172
Legs	44.56 (42.40 to 46.72)	43.22 (40.79 to 45.64)	-1.34 (-2.05 to -0.65)	44.29 (41.60 to 46.99)	42.83 (40.14 to 45.51)	-1.46 (-1.92 to -1.00)	43.83 (40.83 to 46.84)	42.35 (39.28 to 45.42)	-1.48 (-2.14 to -0.83)	0.000	0.918	0.953
Trunk	45.15 (41.84 to 48.47)	43.55 (39.97 to 47.13)	-1.60 (-2.67 to -0.53)	46.75 (44.73 to 48.76)	44.39 (42.70 to 46.08)	-2.36 (-3.33 to -1.38)	47.53 (45.18 to 49.89)	45.59 (42.73 to 48.46)	-1.94 (-2.97 to -0.91)	0.000	0.591	0.589
Body Mass Index, kg/m²	31.20 (29.92 to 32.47)	29.67 (28.28 to 31.06)	-1.53 (-2.02 to -1.03)	30.92 (29.62 to 32.23)	29.20 (27.98 to 30.42)	-1.72 (-2.06 to -1.39)	30.62 (29.05 to 32.18)	29.19 (27.68 to 30.70)	-1.43 (-2.05 to -0.80)	0.000	0.859	0.643
CARDIOMETABOLIC PARAMETERS AND ENERGY METABOLISM												
Glucose, mg/dL	96.06 (93.76 to 98.37)	92.26 (88.20 to 96.31)	-3.80 (-7.50 to -0.12)	97.93 (93.43 to 102.44)	95.58 (91.94 to 99.22)	-2.35 (-7.27 to 2.57)	95.79 (91.82 to 99.76)	92.15 (88.98 to 95.33)	-3.64 (-8.29 to 1.02)	0.013	0.381	0.891
Mean Glucose, mg/dL/120 min	119.90 (109.43 to 130.37)	113.09 (99.70 to 126.48)	-6.81 (-18.50 to 4.87)	116.60 (105.52 to 127.68)	120.79 (107.60 to 133.99)	4.19 (-7.68 to 16.06)	117.02 (108.61 to 125.42)	108.73 (100.05 to 117.41)	-8.29 (-15.22 to -1.36)	0.236	0.666	0.199
Insulin, µIU/mL	36.53 (27.80 to 45.27)	26.56 (19.35 to 33.76)	-9.97 (-14.08 to -5.87)	36.96 (29.30 to 44.62)	31.57 (24.97 to 38.17)	-5.39 (-10.20 to -0.59)	44.94 (36.87 to 53.01)	35.67 (31.29 to 40.04)	-9.27 (-16.92 to -1.63)	0.000	0.134	0.350
HOMA-IR	8.59 (6.59 to 10.59)	6.06 (4.36 to 7.76)	-2.53 (-3.48 to -1.57)	9.00 (7.03 to 10.97)	7.50 (5.74 to 9.25)	-1.50 (-2.98 to -0.03)	10.73 (8.66 to 12.79)	8.09 (7.07 to 9.11)	-2.64 (-4.66 to -0.62)	0.000	0.162	0.489
HOMA-β	416.55 (308.13 to 524.98)	337.17 (252.81 to 421.53)	-79.38 (-131.72 to -27.06)	395.08 (315.61 to 474.55)	345.95 (287.35 to 404.56)	-49.13 (-103.70 to 5.45)	515.32 (405.93 to 624.71)	449.01 (385.98 to 512.05)	-66.31 (-175.37 to 42.76)	0.004	0.052	0.735
Quicki Index	0.29 (0.28 to 0.30)	0.30 (0.29 to 0.31)	0.01 (0.01 to 0.02)	0.28 (0.28 to 0.29)	0.29 (0.28 to 0.30)	0.01 (0.00 to 0.01)	0.28 (0.27 to 0.28)	0.29 (0.28 to 0.29)	0.01 (0.00 to 0.01)	0.000	0.037	0.165
Matsuda Index	3.44 (1.71 to 5.17)	3.76 (2.60 to 4.93)	0.32 (-0.78 to 1.43)	2.22 (1.81 to 2.63)	2.37 (1.85 to 2.90)	0.15 (-0.21 to 0.52)	1.99 (1.27 to 2.72)	2.29 (1.72 to 2.85)	0.30 (-0.48 to 1.07)	0.278	0.147	0.921

Cholesterol, mg/dL												
Total	181.44 (163.76 to 199.12)	168.31 (150.05 to 186.56)	-13.13 (-23.20 to -3.06)	194.81 (173.36 to 216.26)	184.52 (169.07 to 199.97)	-10.29 (-28.65 to 8.08)	196.44 (173.89 to 218.98)	171.50 (154.92 to 188.08)	-24.94 (-44.25 to -5.62)	0.001	0.470	0.498
LDL	111.87 (92.40 to 131.35)	103.78 (85.24 to 122.31)	-8.09 (-15.97 to -0.22)	126.95 (108.13 to 145.76)	120.63 (105.89 to 135.37)	-6.32 (-20.96 to 8.33)	117.39 (96.85 to 137.94)	102.77 (89.03 to 116.50)	-14.62 (-29.85 to 0.60)	0.012	0.329	0.704
HDL	45.18 (41.15 to 49.21)	41.66 (38.03 to 45.29)	-3.52 (-6.56 to -0.48)	48.13 (42.79 to 53.47)	42.72 (37.81 to 47.63)	-5.41 (-9.73 to -1.08)	53.72 (46.76 to 60.69)	46.09 (39.89 to 52.29)	-7.63 (-11.43 to -3.84)	0.000	0.211	0.250
Non-HDL	136.26 (116.59 to 155.92)	126.83 (107.63 to 146.02)	-9.43 (-16.99 to -1.87)	146.68 (126.56 to 166.80)	140.29 (124.60 to 155.98)	-6.39 (-21.39 to 8.60)	142.71 (122.19 to 163.24)	125.25 (111.19 to 139.30)	-17.46 (-34.49 to -0.44)	0.006	0.589	0.612
Triglycerides, mg/dL	121.91 (85.35 to 158.47)	114.32 (78.30 to 150.34)	-7.59 (-16.95 to 1.77)	98.67 (84.74 to 112.59)	97.99 (80.17 to 115.80)	-0.68 (-14.53 to 13.17)	126.61 (99.30 to 153.91)	112.20 (80.62 to 143.78)	-14.41 (-33.61 to 4.80)	0.081	0.309	0.502
β-Hydroxybutyrate, mmol/L	0.11 (0.09 to 0.14)	0.29 (0.11 to 0.48)	0.18 (-0.01 to 0.36)	0.11 (0.07 to 0.14)	0.20 (0.13 to 0.27)	0.09 (0.03 to 0.16)	0.09 (0.05 to 0.13)	0.30 (0.16 to 0.43)	0.21 (0.06 to 0.35)	0.000	0.478	0.277
Resting Metabolic Rate, Kcal/Day	1711.26 (1595.60 to 1826.93)	1641.42 (1517.05 to 1765.79)	-69.84 (-149.13 to 9.45)	1781.17 (1630.21 to 1932.13)	1677.82 (1542.41 to 1813.22)	-103.35 (-167.34 to -39.37)	1794.81 (1662.64 to 1926.99)	1662.87 (1565.22 to 1760.52)	-131.94 (-236.88 to -26.99)	0.000	0.763	0.633
Resting Respiratory Exchange Ratio	0.79 (0.75 to 0.82)	0.75 (0.72 to 0.78)	-0.04 (-0.07 to -0.00)	0.76 (0.74 to 0.79)	0.74 (0.70 to 0.79)	-0.02 (-0.06 to 0.02)	0.77 (0.73 to 0.80)	0.74 (0.69 to 0.78)	-0.03 (-0.08 to 0.02)	0.015	0.677	0.784
Peak Oxygen Consumption, mL/kg/min	25.01 (22.68 to 27.33)	25.32 (21.75 to 28.90)	0.31 (-2.40 to 3.03)	23.87 (21.99 to 25.75)	23.63 (21.89 to 25.38)	-0.24 (-1.80 to 1.32)	26.66 (24.52 to 28.80)	25.95 (23.54 to 28.36)	-0.71 (-2.61 to 1.17)	0.733	0.161	0.822
SUBJECTIVE APPETITE, SLEEP QUALITY, AND RISK OF BINGE EATING												
Hunger, scale 0-100 mm	53 (39 to 66)	43 (32 to 54)	-10 (-24 to 5)	47 (36 to 58)	35 (21 to 49)	-12 (-28 to 5)	51 (38 to 63)	63 (54 to 73)	12 (-1 to 26)	0.511	0.049	0.030

Satiety, scale 0-100 mm	52 (39 to 65)	63 (52 to 73)	11 (-6 to 28)	47 (35 to 59)	62 (46 to 78)	15 (-2 to 33)	49 (35 to 62)	42 (33 to 51)	-7 (-15 to 2)	0.143	0.206	0.032
Desire to eat, scale 0-100 mm	61 (48 to 73)	43 (29 to 57)	-18 (-36 to 1)	55 (44 to 66)	34 (22 to 46)	-21 (-36 to -6)	56 (42 to 70)	66 (55 to 78)	10 (-2 to 23)	0.039	0.070	0.002
Capacity to eat, scale 0-100 mm	66 (54 to 78)	54 (42 to 66)	-12 (-30 to 6)	59 (47 to 71)	45 (33 to 57)	-14 (-28 to -1)	71 (62 to 80)	73 (60 to 86)	2 (-9 to 14)	0.061	0.018	0.126
Binge Eating Disorder, score	15 (12 to 19)	6 (4 to 9)	-9 (-13 to -6)	14 (10 to 19)	8 (6 to 11)	-6 (-9 to -3)	14 (12 to 16)	8 (5 to 10)	-6 (-9 to -4)	0.000	0.975	0.356
Sleep Quality Index	8 (6 to 10)	5 (4 to 6)	-3 (-5 to -2)	8 (6 to 9)	5 (4 to 6)	-3 (-4 to -1)	7 (6 to 9)	5 (3 to 6)	-2 (-4 to -1)	0.000	0.924	0.720

Abbreviations: HDL, high-density lipoprotein; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; TRE, time-restricted eating; QUICKI, quantitative insulin sensitivity check index.

SI conversion factors: To convert total, HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert triglycerides to millimoles per liter, multiply by 0.0113; to convert glucose to millimoles per liter, multiply by 0.0555; and to convert insulin to picomoles per liter, multiply by 6.945.

[a]Data are presented as mean (95% confidence interval, CI). Data analyzed by intention-to-treat analysis (eTRE, dTRE and CG n=16).

eTable 2. Physical Activity by Diet Group and Time Point.

Variable	Early-TRE				Delayed-TRE				Control			
	Habitual	**1-week**	**4-week**	**8-week**	**Habitual**	**1-week**	**4-week**	**8-week**	**Habitual**	**1-week**	**4-week**	**8-week**
Total-MET / min / week[a]	1712 (789 to 2634) n = 12	801 (432 to 1170) n = 13	1090 (310 to 1870) n = 9	1841 (15 to 3667) n = 13	543 (73 to 1013) n = 11	1499 (26 to 2971) n = 10	1102 (343 to 1861) n = 10	736 (270 to 1203) n = 9	1272 (897 to 1647) n = 13	1556 (937 to 2176) n = 11	1858 (966 to 2750) n = 11	1444 (898 to 1990) n = 12
Min / week[b]	-	358 (218 to 498) n = 11	432 (279 to 586) n = 11	323 (211 to 434) n = 12	-	256 (197 to 315) n = 9	320 (199 to 442) n = 11	243 (166 to 321) n = 11	-	320 (165 to 476) n = 10	327 (174 to 479) n = 7	421 (209 to 634) n = 10

Abbreviations: MET, metabolic equivalent.

Data are expressed as mean (95% CI); only observed values included.

[a]IPAQ-SF; Effects of time (p 0.937), group (0.246), and group*time (0.137). Missing data due to errors in sending the IPAQ-SF.
[b]Google Fit; Effects of time (p 0.457), group (0.312), and group*time (0.317). Missing data due to errors in the Google Fit app.

eTable 3. Dietary Intake by Diet Group and Time Point.

Variable	Early-TRE				Delayed-TRE				Control				*Time p value*	*Group p value*	*Time*Group p value*
	Diet (n=13)	**Usual (n=12)**	**4-week (n=11)**	**8-week (n=13)**	**Diet (n=11)**	**Usual (n=10)**	**4-week (n=10)**	**8-week (n=11)**	**Diet (n=13)**	**Usual (n=12)**	**4-week (n=11)**	**8-week (n=13)**			
Kcal[a]	1703 (1596 to 1809)	1800 (1507 to 2093)	991 (841 to 1141)	1016 (887 to 1145)	1734 (1621 to 1848)	1936 (1513 to 2358)	1227 (1039 to 1415)	1031 (880 to 1184)	1727 (1617 to 1837)	1979 (1549 to 2410)	1244 (1057 to 1431)	1101 (982 to 1221)	0.000	0.340	0.173
Carbohydrates (%)[b]	49 (47 to 50)	50 (44 to 55)	51 (47 to 56)	48 (45 to 51)	48 (46 to 49)	46 (42 to 50)	42 (39 to 46)	43 (38 to 47)	49 (48 to 50)	48 (44 to 53)	45 (42 to 49)	44 (38 to 49)	0.140	0.002	0.118
Carbohydrates (g)[c]	207 (192 to 222)	221 (185 to 258)	128 (107 to 148)	124 (107 to 141)	208 (193 to 223)	217 (174 to 260)	132 (106 to 158)	109 (91 to 126)	211 (197 to 225)	237 (182 to 292)	144 (115 to 172)	120 (99 to 142)	0.000	0.749	0.694
Fibers (g)[d]	36 (32 to 40)	14 (11 to 17)	17 (15 to 19)	14 (12 to 16)	39 (34 to 44)	14 (10 to 17)	20 (14 to 26)	15 (10 to 19)	37 (32 to 41)	17 (11 to 22)	20 (14 to 26)	18 (12 to 23)	0.000	0.440	0.401
Protein (%)[e]	23 (22 to 24)	17 (15 to 18)	18 (17 to 20)	22 (21 to 24)	24 (23 to 26)	17 (14 to 19)	24 (22 to 25)	25 (22 to 27)	24 (23 to 25)	18 (15 to 21)	21 (20 to 23)	24 (22 to 27)	0.000	0.012	0.005
Protein (g)[e]	97 (91 to 104)	74 (61 to 86)	46 (38 to 54)	56 (49 to 62)	105 (98 to 113)	78 (59 to 96)	71 (61 to 81)	64 (53 to 74)	102 (94 to 111)	90 (65 to 115)	67 (56 to 77)	67 (57 to 77)	0.000	0.033	0.041
Fat (%)[f]	29 (28 to 31)	33 (29 to 37)	31 (28 to 35)	30 (27 to 32)	28 (27 to 29)	35 (33 to 38)	34 (31 to 38)	32 (29 to 36)	28 (27 to 29)	33 (31 to 36)	33 (31 to 36)	32 (29 to 37)	0.000	0.267	0.441
Fat (g)[g]	55 (51 to 60)	67 (51 to 83)	35 (28 to 42)	34 (30 to 46)	54 (50 to 60)	76 (59 to 94)	47 (40 to 54)	38 (30 to 46)	54 (50 to 58)	74 (56 to 92)	45 (40 to 51)	40 (33 to 47)	0.000	0.236	0.171

Data are expressed as mean and (95% CI); only observed values included. Some 3-day records were not delivered generating missing data (5%).
[a]Significant difference between the usual *vs*. fourth week, and *vs*. eighth week and significant difference between the prescribed *vs*. fourth week, and *vs*. eighth week.
[b]Significant difference between the eTRE group and dTRE group.
[c]Significant difference between the usual *vs*. fourth week, and *vs*. eighth week and significant difference between the prescribed *vs*. fourth week, and *vs*. eighth week.
[d]Significant difference between the prescribed *vs*. usual, *vs*. fourth week, and *vs*. eighth week and significant difference between the fourth week *vs*. usual, and *vs*. eighth week.
[e]Significant difference between the eTRE *vs*. dTRE, and *vs*. control in the fourth week.
[f]Significant difference between the prescribed *vs*. usual, and *vs*. fourth week.
[g]Significant difference between the prescribed *vs*. usual, *vs*. fourth week and *vs*. eighth week and significant difference between the usual *vs*. fourth week and *vs*. eighth week.

CAPÍTULO IV

5 CONSIDERAÇÕES FINAIS E PERSPECTIVAS FUTURAS

A TRE é uma abordagem dietética promissora que promove alterações benéficas em diferentes populações, principalmente em pessoas com excesso de peso. Tal estratégia parece ser capaz de reduzir o peso corporal e trazer melhorias em diversos marcadores sanguíneos, especialmente nos relacionados ao metabolismo da glicose. Em relação a outros parâmetros de risco cardiometabólico, os achados permanecem inconsistentes. Adicionalmente, observou-se que na maioria dos estudos encontrados, a restrição de tempo na alimentação induziu uma diminuição no consumo alimentar, ainda que de forma não-intencional. Por consequência, alguns estudos acabaram por não observar os efeitos da TRE isoladamente, uma vez que uma restrição calórica, mesmo que não intencional, foi verificada. Em adição, observamos que a maioria dos estudos foram realizados exclusivamente ou majoritariamente em homens. Além disso, observou-se uma variedade de protocolos de TRE adotada nos estudos, contendo, por exemplo, distintas durações da janela de alimentação e de jejum, distintos períodos de intervenção, bem como diferentes momentos do dia para realização da alimentação e, consequentemente, do período em jejum. Assim, conclusões acerca dos efeitos da TRE sobre parâmetros de saúde em humanos permanecem limitadas.

Um subtipo de TRE (eTRE) emergiu recentemente como uma estratégia nutricional capaz de promover importantes alterações em marcadores de risco cardiometabólico, especialmente em adultos com obesidade. Tais mudanças positivas parecem ser impulsionadas pelo simples deslocamento da janela de alimentação às primeiras horas do dia e pela manutenção de um jejum robusto nas horas subsequentes. No entanto, pouco é conhecido sobre os efeitos do eTRE em comparação a distintas abordagens de TRE e a um protocolo de dieta tradicional. Encontramos apenas um estudo comparando os efeitos da eTRE aos da dTRE em adultos com obesidade, não sendo observadas diferenças significativas entre as condições de TRE após uma semana.

A fim de contribuir com importantes questões em aberto envolvendo a TRE, decidimos realizar um ensaio clínico randomizado para analisar os efeitos crônicos (8 semanas) da eTRE, da dTRE e da dieta com restrição calórica sem restrição de tempo (controle) sobre parâmetros corporais e metabólicos em adultos com sobrepeso e obesidade. Propomo-nos a investigar se

sob condições similares de restrição calórica, diferentes abordagens de TRE (eTRE e dTRE) e a alimentação sem restrição de tempo exerceriam efeitos distintos.

De forma geral, todos os grupos do presente estudo apresentaram alterações similares após 8 semanas de intervenção, sem quaisquer diferenças estatisticamente significativas entre os protocolos de dieta adotados. Desta forma, sob condições de restrição calórica, não foram observados efeitos superiores ou inferiores dos grupos de TRE (independentemente do momento do dia) em comparação ao grupo controle. Portanto, a TRE mostrou-se como uma abordagem nutricional passível de ser utilizada em indivíduos com obesidade e sem complicações clínicas. Nosso estudo não demonstrou superioridade da eTRE em comparação à dTRE. Embora tenhamos encontrado melhorias mais pronunciadas em marcadores relacionados ao metabolismo da glicose no grupo eTRE, essa diferença não foi estatisticamente significativa em comparação aos demais grupos. Por fim, também observamos reduções adicionais na ingestão alimentar, mesmo sob condições de restrição calórica impostas pela pesquisa. No entanto, esse comportamento verificado em todos os grupos, inclusive no controle que não possuía restrições de tempo na alimentação.

A partir dos achados da revisão narrativa e do estudo experimental, identificamos possíveis questões a serem futuramente exploradas.

1) Estudos futuros devem investigar se uma mesma duração de TRE aplicada em diferentes momentos do dia pode causar adaptações distintas em humanos. Em adição, parece importante investigar os efeitos de uma abordagem de TRE com uma janela alimentar que termine mais tarde (~23:00 - 00:00). Acreditamos que o horário de encerramento adotado em nosso protocolo de dTRE (~20:00) pode não ter sido suficientemente tardio para provocar alterações negativas e / ou impedir mudanças positivas no metabolismo de adultos com obesidade, como alguns estudos anteriores sugerem. É possível que um início atrasado da alimentação em associação ao encerramento tardio da janela alimentar possa de fato ser um agravante para a saúde humana. Supomos que para indivíduos que habitualmente pulam o café da manhã e iniciam a alimentação pelo almoço, a dTRE pode ser utilizada desde que a janela alimentar se encerre no início da noite (~20:00).

2) Outro ponto a ser destacado é a adesão às abordagens de TRE. Em nosso estudo, as desistências ocorridas no grupo eTRE foram em razão da inviabilidade de manter uma janela alimentar com encerramento tão precoce (~16:00). Devido à falta de superioridade estatisticamente significativa desse protocolo em comparação a outros associada à possível dificuldade de mantê-lo por diversas razões (aspectos logísticos, regionais e culturais), a

aplicabilidade da eTRE como estratégia nutricional superior à outras deve ser questionada. Ainda assim, estudos futuros devem analisar os impactos da TRE realizada em diferentes momentos do dia em populações distintas e por períodos de maior duração (6 meses - 1 ano). Além disso, acompanhar os indivíduos após o encerramento da intervenção pode ser importante para identificar efeitos residuais, bem como possíveis reações compensatórias dessa abordagem em longo prazo.

3) Em nosso estudo, mesmo com margens delimitadas de janela alimentar juntamente à dieta hipocalórica, identificamos uma diminuição além do esperado na ingestão energética dos participantes. Embora nosso estudo seja o primeiro a investigar a TRE associada com prescrição de dieta hipocalórica em indivíduos com obesidade, nos questionamos se este comportamento poderia ocorrer em outros estudos, e em que populações essa redução acentuada na ingestão alimentar poderia trazer benefícios. Indivíduos com graus mais severos de obesidade que possuem dificuldades em aderir uma dieta tradicional poderiam encontrar facilidade em diminuir drasticamente o consumo energético por meio da dieta hipocalórica embutida em uma janela alimentar reduzida. Ainda assim, é importante também investigar se tal estratégia traria eventos adversos quando aplicada a estas populações.

4) Visto que tanto uma alimentação adequada quanto a presença do exercício físico são estratégias recomendadas para a melhora da saúde em pessoas com sobrepeso e obesidade, futuros estudos poderiam investigar os efeitos destas duas estratégias combinadas no peso e composição corporal, bem como parâmetros e marcadores relacionados à saúde.