Time Restricted Feeding (4-hour versus 6-hour) for Weight Loss in Obese Adults

BY

Sofia Cienfuegos
B.S., Universidad del Desarrollo, 2013
M.S., University of Illinois at Chicago, 2018

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology and Nutrition in the Graduate College of the
University of Illinois at Chicago, 2021

Chicago, Illinois

Defense Committee:

Krista A. Varady, Chair and Advisor, Kinesiology and Nutrition, UIC
Zhenyuan Song, Kinesiology and Nutrition, UIC
Lisa Tussing-Humphreys, Kinesiology and Nutrition, UIC
Kelsey Gabel, Kinesiology and Nutrition, UIC
Surabhi Bhutani, Exercise and Nutrition, San Diego State University

This thesis is dedicated to my family. Not only to the living but also to those who have passed, who have guided me on each step of my academic career. To my loving and supportive husband, Pablo. He was the one who encouraged me to get my Ph.D. in the first place. Even when our migratory situation here in the US was uncertain, he has always believed in me and helped me push harder and reach my goals. You are the best thing that has happened to me. My best friend, Olivia, has given me the encouragement and mentorship needed since we were four years old. You are my favorite person in this world, and I would not have been able to do any of this without you. To my Chicago family, Caro and Francisco, I want to thank you for your constant support during these years, cheering for me each step of the way. To my Dad, thanks for guiding and showing me the value of knowledge and education. You are my greatest inspiration of a true scholar. To my siblings Samantha, Macarena, Henry, and Mathias, for loving and caring for me like a real sister since the day I was born. Finally, I want to dedicate this thesis to my mom. She is the one that made all of this possible. Thank you for loving and supporting me in such a selfless manner. You are my forever angel, and I hope I can always make you proud.

ACKNOWLEDGMENTS

I want to start by acknowledging the crucial role Dr. Krista Varady has played during my entire Ph.D. program. She opened the doors of her lab during a problematic period of academic uncertainty that I was going through. She immediately took my anxiety away by clarifying every step I needed to take to get my Ph.D. Every week during our in-person meetings and journal clubs, she patiently explained every single detail about the world of clinical trials and obesity research. Finally, I got the confidence to run a clinical trial by myself. This is what a true scholar is, teaching and guiding while still giving full freedom to explore things your way. Her mentoring style is a massive inspiration for my future career; humble, caring, and challenging but always with a good sense of humor. I also want to thank Dr. Giamila Fantuzzi for her tremendous help and guidance during my initial ambiguous period and her support during the COVID pandemic, when international students were having difficulties. I would also like to thank my thesis committee, Dr. Zhenyuan Song, Dr. Lisa Tussing Humphreys, Dr. Kelsey Gabel, and Dr. Surabhi Bhutani, for their commitment to my success and overseeing my thesis defense.

I was lucky enough to have some genuinely fantastic lab mates. They guided me step-by-step on how to run a clinical trial productively. As an international student just starting my Ph.D. program, I was unaware of several necessary details for my trial's success. Dr. Faiza Kalam and Dr. Kelsey Gabel gave me all the help and training needed to run my clinical trial smoothly. Also, they accompanied me during early mornings to make sure I had a backup in case of a problematic blood draw or any other obstacles. They did not just help with my nervousness during this trial, but they also gave me all the support, mentorship, and guidance throughout my entire Ph.D. program. I am honored to call them friends.

I want to give a special acknowledgment to all the student volunteers that helped with this project. I could always count on Mark Ezpeleta and Vicky Pavlou to arrive very early in the morning with the positivity to help with anything needed. I would also like to acknowledge Shuhao Lin and Manoela Olivera for all their help with analyzing food records and other study questionnaires. Their excellent work truly exemplifies the quality of students that this program has.

SC

CONTRIBUTION OF AUTHORS

Manuscript 1 represents a published manuscript (Cienfuegos, Sofia, et al. "Effects of 4-and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity." Cell metabolism 32.3 (2020): 366-378.) for which I was the first author. I conducted the clinical trial, analyzed the data, performed the statistical analysis, and wrote the manuscript. Kelsey Gabel, Faiza kalam, Mark Ezpeleta, Eric Wiseman and Vasiliki Pavlou helped with conducting the clinical trial and coordinating participants visits. Shuhao Lin and Manoela Lima Oliveira helped with the analysis of food records. My research mentor Krista Varady designed the research, analyzed the data, and wrote the manuscript. Manuscript 2 represents a published manuscript (Cienfuegos, Sofia, et al. "The effect of 4-h versus 6-h time restricted feeding on sleep quality, duration, insomnia severity and obstructive sleep apnea in adults with obesity." Nutrition and Health (2021): 02601060211002347.) for which I was the first author and designed the research, conducted the clinical trial, analyzed the data, performed the statistical analysis, and wrote the manuscript. Kelsey Gabel, Faiza Kalam, Mark Ezpeleta, Vasiliki Pavlou, Shuhao Lin, and Erik Wiseman assisted with the conduction of the clinical trial. Finally, my mentor Krista Varady designed the research, analyzed the data, and wrote the manuscript.

Contents

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADF	Alternate day fasting
BMI	Body mass index
CHD	Coronary heart disease
CR	Calorie Restriction
CVD	Cardiovascular disease
HDL	High-density lipoprotein
IR	Insulin Resistance
IF	Intermittent Fasting
ISI	Insomnia Sleep Index
LDL	Low-density Lipoprotein
PSQI	Pittsburg Sleep Quality Index
RMR	Resting metabolic rate
SEM	Standard error of the mean
T2DM	Type Two Diabetes Meletus
TRF	Time-restricted feeding
WC	Waist circumference

SUMMARY

Time restricted feeding (TRF) is a form of intermittent fasting that has gained substantial popularity over recent years as a weight loss regimen. Despite its growing popularity, very few studies have examined the weight loss efficacy of this diet. TRF involves eating within a specific window of time each day, and water fasting for the rest of the day. The goal of this study was to compare the effects of a 4-h TRF versus 6-h TRF on body weight, metabolic disease risk factors, inflammation, and sleep, in adults with obesity. Subjects with obesity (n = 58) were randomized to 1 of 3 groups: 1) 4-h TRF (ad libitum feeding between 3pm to 7pm, water fasting between 7pm to 3pm), 2) 6-TRF (ad libitum feeding between 1pm to 7pm, water fasting between 7pm to 1pm), or 3) control group (usual diet with no meal timing restrictions) for 8 weeks. Results from this study show that 8 weeks of 4-h and 6-h TRF decreases body weight by -3.2% and -3.2%, respectively, relative to controls. Subjects were adherent to the prescribed eating window on 6.2 days per week, and this level of adherence remained constant throughout the 8-week trial. Our findings also indicate that reducing the daily eating window to either 4-h or a 6-h decreases caloric intake by ~550 kcal/d, without intentional calorie counting. Both TRF interventions produced significant reductions in fasting insulin, HOMA-IR (measurement of insulin resistance) and oxidative stress, versus controls. However, other metabolic disease risk parameters such as plasma lipids, blood pressure, and inflammation, remained unchanged. As for sleep, sleep quality and duration remained unchanged in all groups. Our results also suggest that TRF is a safe diet therapy that does not induce any significant adverse effects. These data offer promise for the use of shorter (4-h and 6-h) eating windows as safe and effective weight loss regimens in adults with obesity. However, longer-term, larger-scale randomized controlled trials will be required before solid conclusions can be reached.

INTRODUCTION

Background and Rationale:

Modest weight loss of 5-10% is sufficient to reduce metabolic disease risk in obese individuals. The first line of therapy prescribed for weight loss is daily calorie restriction (CR; 25% restriction every day). However, adherence to CR greatly diminishes after 4-6 weeks due to subject frustration with constantly having to count calories and never eat freely. Considering these issues with CR, one approach that limits food intake timing, instead of the number of calories consumed, has been developed. This strategy is termed time-restricted feeding (TRF) and involves confining the period of food intake to 8 h/d (10 am to 6 pm) without calorie counting. Preliminary findings of 8-h TRF demonstrate modest weight loss (2.5%) and blood pressure reductions after 12 weeks [1]. However, what remains unknown is whether shorter feeding windows during TRF (such as 4-h or 6-h feeding windows) can produce even more significant weight loss in obese adults. Also of interest is the impact of these shorter feeding windows on metabolic disease risk indicators, such as plasma lipids, blood pressure, insulin resistance, and oxidative stress. The effect of these diets on sleep quality and duration is also of great interest.

To test the study objectives, a 10-week randomized, controlled, parallel-arm trial, divided into two consecutive periods: (1) 2-week baseline period; and (2) 8-week TRF weight-loss period, was implemented. Obese subjects (n = 57) were randomized to 1 of 3 groups: (1) 4-h TRF, (2) 6-h TRF, or (3) a no-intervention control group. This study is the first randomized controlled trial of 4-h versus 6-h TRF to test the hypothesis that the 4-h TRF diet produces greater body weight reductions versus a 6-h TRF diet. Due to these greater decreases in body weight, the 4-h TRF

diet will also produce greater improvements in metabolic disease risk factors (plasma lipids, blood pressure, glucoregulatory factors, inflammation and oxidative stress), and sleep, when compared to the 6-h TRF diet. The specific aims of the study are as follows:

Specific Aims

Specific Aim 1: To compare the effects of 4-h versus 6-h time restricted feeding (TRF) on body weight and body composition in adults with obesity.

> **Hypothesis 1:** The 4-h TRF diet will produce greater decreases in body-weight, fat mass, and visceral fat mass versus the 6-h TRF diet after 8 weeks in adults with obesity. Lean mass will remain unchanged in both groups.

Specific Aim 2: To compare the effects of 4-h versus 6-h TRF on metabolic disease risk factors in adults with obesity.

> **Hypothesis 2:** The 4-h TRF diet will produce greater decreases in fasting insulin, fasting glucose, insulin resistance (measured by HOMA-IR), triglycerides, and blood pressure versus the 6-h TRF diet after 8 weeks, due to greater weight loss by 4-h TRF.

Specific Aim 3: To compare the effects of 4-h versus 6-h time TRF on markers of inflammation and oxidative stress.

> **Hypothesis 3:** The 4-h TRF diet will produce greater decreases in tumor-necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and 8-isoprostane versus the 6-h TRF diet after 8 weeks, due to greater weight loss by 4-h TRF.

Specific Aim 4: To compare the effects of 4-h versus 6-h TRF on sleep quality and duration in adults with obesity.

Hypothesis 4: The 4-h TRF diet will improve self-reported sleep quality and duration to a greater extent versus the 6-h TRF diet after 8 weeks, due to greater weight loss by 4-h TRF.

Significance

Our study is the first randomized controlled trial to compare the weight loss efficacy of 4-h versus 6-h TRF in adults with obesity. Findings from this trial will provide evidence that 4-h TRF produces superior weight loss and more pronounced improvements in metabolic disease risk factors and sleep, versus 6-h TRF, in this population group. This study will also show that TRF can be used as an effective non-pharmacological therapy to improve insulin resistance and decrease metabolic risk in adults with obesity.

II. LITERATURE REVIEW

Introduction

The world health organization (WHO) declared obesity a modern age epidemic. More than 70 million Americans are currently struggling with obesity and the comorbidities associated with this disorder. Throughout the decade, researchers and health professionals have been looking for strategies to reduce the worldwide rising body mass index (BMI) curve. While calorie restriction seems like a simple approach to weight loss, most patients are unable to follow calorie restriction (CR) diets for long periods of time. The main barriers are, dissatisfaction with counting calories, the exclusion of certain foods or food groups and the overall frustration of being unable to engage in social activities that involve food. Intermittent fasting (IF) is an alternative approach to CR that started gaining popularity a decade ago and still gains more and more supporters each day. There are two main types of IF: alternate day fasting (ADF) and time restricted feeding (TRF).

ADF is one of the first methods to be described in the IF literature. It involves alternating feasting and fasting days. This way, patients can still enjoy their traditional eating habits and engage in social interactions every other day. There are two main types of ADF: (1) zero-calorie ADF (a zero-calorie fast day alternated with an ad libitum intake feast day), and (2) modified ADF (500-600 kcal fast day alternated with an ad libitum intake feast day). TRF is one of the newest forms of IF. It involves eating within a window of time each day, rather than alternating

calorie allowances each day. The main benefit of TRF is that patients do not have to count calories during their eating window. The eating windows can range from 4 to 10 hours/day.

The goal of this review is to summarize the effects of ADF and TRF on body weight, body composition, metabolic disease, inflammatory markers, and sleep. The safety of these diets will also be reviewed.

Body weight and Body Composition

The effects of ADF and TRF on body composition are reported in **Table 1**.

ADF

Zero calorie ADF produces between 5 and 9% weight loss in 8 weeks and decreases in fat mass, fat free mass and visceral fat. Short term ADF shows a 5-8% weight loss in 8 weeks with considerable reductions in fat mass and visceral fat, while preserving fat free mass. Long term ADF produces between 5 and 8% weight loss with substantial reductions in fat mass, fat free mass and visceral fat. Stekovic et al. [1], Cho et al. [2] Bhutani et al. [3] Trepanowski et al. [4] and Varady et al. [5] demonstrate significantly greater reductions in fat mass when compared to controls but not significantly greater than CR. As for lean mass, half of the studies showed a within group decrease in lean mass. Coutinho et al. [6] compared ADF to CR in 35 obese participants for 12 weeks and was the only study that showed a within group increase in lean mass. ADF was effective in decreasing visceral fat in most studies, but not significantly greater than CR. Stekovic et al. [1] compared zero calorie ADF to a control group in 57 healthy

participants for four weeks, showing significantly greater reductions in the ADF group compared to controls. Trepanowski et al. [4] compared ADF with CR and controls in 100 obese subjects for 24 weeks showing significantly greater reductions in visceral fat in the ADF group when compared to controls but not to CR. In conclusion, ADF induces significant reductions in body weight, fat mass, which are comparable to CR, but not superior. In terms of fat free mass, most studies show either a decrease or maintenance, rather than an increase, in this body composition parameter.

TRF

The majority of TRF studies show approximately a 2-3% weight loss after 8 weeks of intervention. Gabel et al. [7] compared an 8-h TRF with a historical control in 23 obese subjects for 12 weeks showing a 3% weight loss that was achieved in the TRF group in the absence of CR. Also, Wilkinson et al. [8] examined the effect of a 10-h TRF in 19 subjects with metabolic syndrome, showing a 3% weight loss after 12 weeks, without CR.

Only half of the studies show a significant within group decrease in fat mass. Moro et al. [9] compared 8-h TRF versus controls in 34 healthy active males achieving a significantly greater fat loss compared to controls after 8 weeks. As for fat free mass, TRF trials show either an increase or preserved fat free mass rather than a reduction. McAllister et al. [10] compared 8-h TRF ad libitum versus 8-h TRF isocaloric in 22 healthy males for 4 weeks, showing an increase in fat free mass in both groups but significantly greater in the ad libitum group. Also, Tinsley et al. [11] compared an 8-h TRF versus controls in 40 healthy active females, showing a within group

increase in fat free mass in the TRF group. Finally, most studies of TRF show no effect on visceral fat mass. Only Wilkinson et al. [8] showed a within group decrease in visceral fat after 12 weeks of 10-h TRF.

In conclusion, TRF produces 2-3% reductions in body weight accompanied by decreases in fat mass, in the absence of CR. The effects of TRF on fat free mass and visceral fat mass are less clear. However, the body of literature has several aspects that might cause confounding factors. For instance, most of the samples used in these studies were either participants with metabolic disorders (diabetes, prediabetes) or healthy trained young individuals, making it difficult to draw conclusions from such a variable population. Also, most of these studies were short, had very small sample sizes, and lacked control groups.

Summary: Body weight and Body Composition

ADF and TRF are both effective weight loss strategies in adults with obesity, but ADF appears to produce greater weight loss (3-7%) versus TRF (2-3%) after short intervention periods (8-12 weeks). In terms of body composition, both ADF and TRF produce significant fat mass reductions, but ADF produces a more pronounced fat mass loss. Neither diet has any substantial effect on fat free mass or visceral fat mass.

Table 1: The Effect of ADF and TRF on Body Composition.

Reference	Design	Intervention	Subjects	Length	%BW change	FM	FFM	VF
ADF (100% energy restriction on fast day)								
*** Heilbronn, L. K. et al. 2005** [12]	Longitudinal Trial	Zero Calorie ADF	N= 16 Normal/Overw Male/Female	3 weeks	2%	--	--	--
*** Stekovic, S. et al. 2019** [1]	RCT	1. Zero Calorie ADF 2. Control	N= 57 Healthy Male/Female	4 weeks	1. – 5%*† 2. Ø	1. ↓*† 2. Ø	1. ↓*† 2. Ø	1. ↓*† 2. Ø
*** Hutchison, A. T. et al. 2019** [13]	RCT	1. ADF 70 2. ADF 100 3. CR 70 4. Control	N= 88 Overw/Obese Female Only	8 weeks	1. – 6%*† 2. – 3%*† 3. – 4% 4. Ø	1. ↓*† 2. ↓* 3. ↓* 4. Ø	1. ↓* 2. Ø 3. Ø 4. Ø	--
Catenacci, V. A. et al. 2016 [14]	Randomized trial	1. Zero calorie ADF 2. CR	N= 26 Obese Male/Female	8 weeks + 24 weeks FU	1. - 9%* 2. - 6%*	1. ↓* 2. ↓*	1. ↓* 2. ↓*	1. ↓* 2. ↓*
ADF (25% energy restriction on fast day)								
*** Harder-Lauridsen, N. M. et al. 2017** [15]	Randomized Trial	1. ADF + Bed Rest 2. Bed Rest.	N= 20 Healthy Male Only	1 week	1. – 3%* 2. – 2%*	Ø	1. ↓* 2. ↓*	--
*** Hoddy, K. K. et al. 2016** [16]	Longitudinal Trial	ADF	N= 59 Obese Male/Female	8 weeks	- 4%	↓*	↓*	↓*
*** Cho, A. R. et al. 2019** [2]	RCT	1. ADF 2. Exercise 3. ADF + Exercise 4. Control	N= 31 Overw/Obese Male/Female	8 weeks	1. – 5%*† 2. – 3%* 3. – 5%*† 4. Ø	1. ↓*† 2. ↓ 3. ↓*† 4. Ø	Ø	Ø
*** Varady, K. A. et al. 2015** [17]	Randomized Trial	1. ADF-HF (45% fat) 2. ADF-LF (25% fat)	N= 29 Obese Female Only	8 weeks	1. – 5%* 2. – 5%*	1. ↓* 2. ↓*	--	--
*** Johnson, J. B. et al 2007** [18]	Longitudinal Trial	ADF	N= 10 Asthma Obese Male/Female	8 weeks	- 8%	--	--	--

Varady, K. A. et al. 2009 [19]	Longitudinal trial	1. 2w control 2. 4w ADF controlled 3. 4w ADF self-selected	N= 16 Obese Male/Female	10 weeks	- 6%*	1. ↓* 2. ↓* 3. ↓*	Ø	--
Hoddy, K. K.et. al. 2014 [20]	RCT	1. ADF Lunch 2. ADF Dinner 3. ADF small meals	N= 74 Obese Male/Female	10 weeks	1. - 4% * 2. - 4% * 3. - 5% *	1. ↓* 2. ↓* 3. ↓*	1. ↓* 2. ↓* 3. ↓*	1. ↓* 2. ↓* 3. ↓*
*** Klempel, M. C. et al 2013** [21]	Randomized Trial	1. ADF-HF (high fat) 2. ADF-LF (low fat)	N= 35 Obese Male/Female	10 weeks	1. - 5%*† 2. - 4%*	1. ↓* 2. ↓*	Ø	--
Bhutani, S. et al. 2013 [3]	RCT	1. ADF + Exercise 2. ADF 3. Exercise 4. Control	N= 64 Obese Male/female	12 weeks	1. - 6%*† 2. - 3%* 3. - 1% 4. Ø	1. ↓*† 2. Ø 3. Ø 4. Ø	Ø	1. ↓* 2. ↓* 3. ↓* 4. Ø
Varady, K. A. et al. 2013 [5]	RCT	1. ADF 2. Control	N= 32 Healthy/Overw Male/Female	12 weeks	1. - 5% *† 2. Ø	1. ↓*† 2. Ø	Ø	--
Coutinho, S. R. et al. 2018 [6]	RCT	1. ADF 2. CR	N= 35 Obese Male/Female	12 weeks	1. - 12%* 2. - 12%*	1. ↓* 2. ↓*	1. ↑* 2. ↑*	--
Kalam, F. et al. 2019 [22]	Longitudinal trial	ADF + low carb	N= 31 Obese Male/Female	12 weeks + 12 weeks WM	- 6%	↓*	Ø	Ø
Bowen, J. et. al. 2018 [23]	Randomized trial	1. ADF + CR 2. CR	N= 162 Obese Male/Female	16 weeks + 8 weeks WM	1. - 10%* 2. - 12%*	1. ↓* 2. ↓*	1. ↓* 2. ↓*	1. ↓* 2. ↓*
Trepanowski, J. F. et. al. 2017 [4]	RCT	1. ADF 2. CR 3. Control	N= 100 Overw/Obese Male/Female	24 weeks + 24 weeks WM	1. - 6%*† 2. - 5%*† 3. Ø	1. ↓*† 2. ↓*† 3. Ø	1. ↓* 2. ↓* 3. ↑*	1. ↓*† 2. ↓*† 3. Ø
*** Gabel, K. et al. 2019** [24]	RCT	1. ADF 2. CR 3. Control	N= 43 IR Obese Male/Female	24 weeks	1. – 10%*† 2. – 8%*† 3. Ø	1. ↓*† 2. ↓*† 3. Ø	Ø	Ø
TRF 4-6 h								
*** Arnason, T. G. et al. 2017** [25]	Longitudinal Trial	1. TRF (4-6 h)	N= 10 type 2 Diabetic Overw/Obese Male/Female	2 weeks	- 1%	--	--	--

Tinsley, G. M. et al. 2017 [26]	RCT	1. TRF (4h) + Exercise 2. Exercise	N= 18 Healthy Active Male Only	8 weeks	Ø	Ø	Ø	--
TRF 7-10 h								
*** Hutchison, A. T. et al. 2019** [27]	Crossover Trial	1. TRFe (9h) 2. TRFd (9h)	N=15 Prediabetic Overw/Obese Male Only	1 week	1. – 1%* 2. – 1%*	Ø	Ø	Ø
*** McAllister, M. J. et al. 2019** [10]	Randomized Trial	1. TRF (8h) ad libitum. 2. TRF (8h) iso-caloric.	N= 22 Healthy Male Only	4 weeks	1. ↓* 2. ↓* (No percent)	1. ↓* 2. ↓*	1. ↑† 2. ↑	--
Moro, T. et al. 2016 [9]	Randomized Trial	1. TRF (8h) 2. Control	N= 34 Healthy Active Male Only	8 weeks	Ø	1. ↓*† 2. Ø	Ø	--
Tinsley, G. M. et al. 2019 [11]	RCT	1. TRF (8h) 2. TRF (8h) + HMB 3. Control	N= 40 Healthy Active Female Only	8 weeks	1. + 1%* 2. + 1%* 3. + 2%*	1. ↓ 2. ↓* 3. Ø	1. ↑* 2. ↑* 3. ↑*	--
Gabel, K. et al. 2018 [7]	Randomized Trial	1. TRF (8h) 2. Control (historical)	N= 23 Obese Male/Female	12 weeks	1. -3%*† 2. Ø	Ø	Ø	Ø
Kesztyus, D. et al.2019 [28]	Longitudinal Trial	TRF (8-9 h)	N= 40 Overw Obese Male/Female	12 weeks	2%	--	--	--
Wilkinson, M. J. et al 2020 [8]	Longitudinal Trial	TRF (10h)	N= 19 Metabolic syndrome Overw/Obese Male/Female	12 weeks	- 3%*	↓*	Ø	↓*

∅: Non-significant change

* P < 0.05, Significantly different from baseline (within group effect).

† P < 0.05, Significantly different from the control or comparison group (between group effect).

Abbreviations: BW: Body weight. FM: Fat mass. FFM: Fat free mass. VF: Visceral fat. RCT: Randomized controlled trial. CR: Caloric restriction. ADF: Alternate day fasting. TRF: Time restricted feeding.

Metabolic Markers

The effects of ADF and TRF on metabolic markers are reported in **Table 2.**

ADF

Glucoregulation: ADF appears to have favorable effects on glucoregulation. In terms of fasting glucose, Hoddy et al. [16], Cho et al. [2] and Bowen et al. [23] show a within group decrease in fasting glucose. Hutchison et al. and Bhutani et al. show a significant decrease in glucose when compared to CR and control [3, 13]. Similarly, half of ADF studies show a within group decrease in fasting insulin but only Hutchison et al. [13] and Gabel et al. [29] show a significant decrease when compared to CR. However, Gabel et al. subjects were insulin resistant, increasing the chance of showing significant reductions. Hutchison et al. [13] and Trepanowski et al [4] demonstrate significant reductions in the homeostatic model assessment of insulin resistance (HOMA-IR) when compared to CR. Finally, only Harder-Lauridsen et al. [15] and Kalam et al. [22] measured HbA1c, and both of these trials show no effect of ADF on HbA1c.

Lipids: The effect of ADF on serum lipids has been tested in several recent studies. More than half of the ADF studies reviewed here show a within group decrease in LDL cholesterol. Stekovic et al. [1], and Hutchison et al. [13] show significant reductions in LDL cholesterol when compared to controls and CR. Both studies involved a zero-calorie ADF, suggesting this diet might be superior to modified ADF (500 kcal on the fast day) in decreasing LDL cholesterol. Five studies demonstrate a within group increase in HDL, but only Trepanowski et al. [4] show a significantly greater result compared to CR without including physical activity in the

intervention. More than half of these studies show a within group decrease in triglycerides and Stekovic et al[1], Hutchison et al. [13] and Varady et al. [5] show a significantly greater decrease in triglycerides when compared to CR and controls.

TRF

Glucoregulation: TRF shows promising results in terms of ameliorating glucoregulation. Approximately half of TRF studies reviewed here were performed in subjects with either type 2 diabetes or other metabolic disorders such as prediabetes and metabolic syndrome. Most of these TRF studies show a within group decrease in fasting glucose, but Jameshed et al. [30] and Kahleova et al. [31] show significantly lower glucose levels. Approximately one third of TRF studies reviewed here show a within group decrease in fasting insulin. Jameshed et al. [30] and Sutton et al. [32] show significantly greater reductions in fasting insulin and HOMA-IR compared to controls. Sutton et al. [32] compared early TRF (eating all food before 3pm) versus controls (no meal timing restrictions) in prediabetic males for 5 weeks showing statistically greater reductions in insulin and HOMA-IR in the early TRF group. From the four studies that measured HbA1c, only Kesztyus et al. [28] showed a within group reduction. This was a longitudinal trial analyzing the effects of 8-9-h TRF in obese participants for 12 weeks.

Lipids: TRF appears to have conflicting results regarding serum lipids. Wilkinson et al. [8] was the only study that showed a decrease in LDL cholesterol. They analyzed the effect of a 10-h TRF in obese participants with metabolic syndrome for 12 weeks, showing significant reductions only in LDL cholesterol. In contrast, Jameshed et al. [30], Carlson et al. [33], McAllister et al. [10] and Kahleova et al. [31] demonstrate a significant increase in LDL when compared to controls or other forms of TRF. Carlson et al. [33] compared 1 meal in a 4h window versus 3 meals in a 4 h window, while McAllister et al. [10] compared ad libitum versus an isocaloric 8-h window and Kahleova et al. [31] compared a TRF 2-meals versus 6-meals. The 1 meal group, ad libitum and 2 meal group respectively, showed a significant increase in LDL cholesterol, suggesting that less frequent meals during the window will likely alter LDL cholesterol levels. Another explanation for the increase in LDL cholesterol in these studies, could be the lack of CR in these intervention groups. Three studies show a within group increase in HDL cholesterol, but Jameshed et al. [30] and Carlson et al. [33] show significantly greater increases in HDL cholesterol than controls or the 3-meal group. Finally, Moro et al [9] and Kahleova et al. [31] show significantly lower triglycerides levels than controls or TRF 6-meals.

Table 2 *The Effect of ADF and TRF on Metabolic Markers*

Reference	Design	Intervention	Subjects	Length	Glucose	Insulin	IR	A1c	LDL	HDL	TG
ADF (100% energy restriction on fast day)											
Heilbronn, L. K. et al. 2005 [12]	Longitudinal Trial	ADF	N= 16 Healthy/Overw Male/Female	3 weeks	Ø	Ø	--	--	--	--	--
*** Stekovic, S. et al. 2019** [1]	RCT	1. ADF 2. Control	N= 57 Healthy Male/Female	4 weeks	--	--	--	--	1. ↓*† 2. Ø	Ø	1. ↓*† 2. Ø
Hutchison, A. T. et al. 2019 [13]	RCT	1. ADF 70 2. ADF 100 3. CR 70 4. Control	N= 88 Overw/Obese Female Only	8 weeks	1. ↓*† 2. ↓ 3. Ø 4. Ø	1. ↓*† 2. ↑*† 3. Ø 4. Ø	1. ↓*† 2. Ø 3. Ø 4. Ø	--	1. ↓*† 2. Ø 3. Ø 4. Ø	Ø	1. ↓*† 2. Ø 3. Ø 4. Ø
*** Catenacci, V. A. et al. 2016** [14]	Randomized trial	1. ADF 2. CR	N= 26 Obese Male/Female	8 weeks +24 weeks FU	1. ↑* 2. Ø	Ø	--	--	1. ↓* 2. ↓*	1. ↓* 2. ↓*	1. ↓* 2. Ø
ADF (25% energy restriction on fast day)											
Harder-Lauridsen, N. M. et al. 2017 [15]	Randomized Trial	1. ADF + Bed Rest. 2. Bed Rest.	N= 20 Healthy Active Male Only	1 week	Ø	1. ↑*† 2. Ø	1. ↑*† 2. Ø	Ø	1. ↑* 2. ↑*	1. ↓* 2. ↓*	Ø
Varady, K. A. et al. 2015 [17]	Randomized Trial	1. ADF-HF 2. ADF-LF	N= 29 Obese Female Only	8 weeks	Ø	--	--	--	1. ↓* 2. ↓*	Ø	1. ↓* 2. ↓*
Hoddy, K. K. et al. 2016 [16]	Longitudinal Trial	ADF	N= 59 Obese Male/Female	8 weeks	↓*	↓*	--	--	--	--	--
Cho, A. R. et al. 2019 [2]	RCT	1. ADF 2. Exercise 3. ADF + Exercise 4. Control	N= 31 Overw/Obese Male/Female	8 weeks	1. ↓* 2. Ø 3. ↓* 4. Ø	1. Ø 2. Ø 3. Ø 4. ↑*	1. Ø 2. Ø 3. Ø 4. ↑*	--	1. Ø 2. ↑* 3. Ø 4. Ø	1. Ø 2. ↑* 3. Ø 4. ↑*	1. ↑† 2. ↓† 3. ↓* 4. ↑*†
*** Johnson, J. B. et al. 2007** [18]	Longitudinal Trial	ADF	N= 10 Asthma Obese	8 weeks	Ø	Ø	--	--	Ø	↑*	↓*

			Male/Female								
Klempel, M. C. et al. 2013 [21]	Randomized Trial	1. ADF-HF 2. ADF-LF	N= 35 Obese Male/Female	10 weeks	--	--	--	--	1. ↓* 2. ↓*	Ø	1. ↓* 2. ↓*
*** Varady, K. A. et al. 2009** [19]	Longitudinal trial	1. 2w control 2. 4w ADF cont. 3. 4w ADF self-sel.	N= 16 Obese Male/Female	10 weeks	--	--	--	--	1. Ø 2. ↓*† 3. ↓*†	Ø	1. Ø 2. ↓* 3. ↓*†
*** Hoddy, K. K. et al. 2014** [20]	RCT	1. ADF Lunch 2. ADF Dinner 3. ADF small meals	N= 74 Obese Male/Female	10 weeks	Ø	Ø	Ø	--	Ø	Ø	Ø
***Varady, K. A. et al. 2013** [5]	RCT	1. ADF 2. Control	N= 32 Healthy/Overw Male/Female	12 weeks	--	--	--	--	1. ↓* 2. Ø	Ø	1. ↓† 2. Ø
*** Bhutani, S. et al. 2013** [3]	RCT	1. ADF + Exercise 2. ADF 3. Exercise 4. Control	N= 64 Obese Male/female	12 weeks	1. ↓*† 2. ↓*† 3. ↓* 4. Ø	Ø	Ø	--	1. ↓* 2. Ø 3. Ø 4. Ø	1. ↑* 2. Ø 3. Ø 4. Ø	Ø
*** Kalam, F. et. al. 2019** [22]	Longitudinal trial	ADF + low carb	N= 31 Obese Male/Female	12 weeks + 12 weeks WM	Ø	↓*	Ø	Ø	↓*	↑*	Ø
*** Bowen, J. et al. 2018** [23]	Randomized trial	1. ADF + HP + CR 2. CR HP	N= 162 Obese Male/Female	16 weeks + 8 weeks WM	1. ↓* 2. ↓*	1. ↓* 2. ↓*	--	--	1. ↓* 2. ↓*	1. ↓* 2. ↓*	1. ↓* 2. ↓*
Gabel, K. et al. 2019 [24]	RCT	1. ADF 2. CR 3. Control	N= 43 IR Obese Male/Female	24 weeks	Ø	1. ↓*† 2. ↓* 3. ↓*	1. ↓*† 2. ↓* 3. ↓*	--	Ø	Ø	Ø

*** Trepanowski, J. F. et al. 2018**[34]	RCT	1. ADF 2. CR 3. Control	N= 100 Overw/Obese Male/Female	24 weeks	Ø	1. ↓* 2. ↓* 3. Ø	1. ↓*† 2. ↓* 3. Ø	--	--	--	--
*** Trepanowski, J. F. et al. 2017** [4]	RCT	1. ADF 2. CR 3. Control	N= 100 Overw/Obese Male/Female	24 weeks + 24 weeks WM	Ø	Ø	Ø		Ø	1. ↑† 2. ↑ 3. Ø	Ø
TRF 4-6 h											
Jamshed, H. et al. 2019 [30]	Crossover Trial	1. TRF (6h) 2. Control (12h)	N= 11 Overweight Male/Female	4 days	1. ↓*† 2. ↓	1. ↓*† 2. ↓	1. ↓*† 2. ↓	--	1. ↑ *† 2. Ø	1. ↑ † 2. Ø	Ø
Arnason, T. G. et al. 2017 [25]	Longitudinal Trial	TRF (4-6h)	N= 10 type 2 Diabetic Overw/Obese Male/Female	2 weeks	↓*	Ø	Ø	--	--	--	--
Sutton, E. F. et al. 2018 [32]	Crossover Trial	1. TRF e(6h) 2. Control (12 h)	N= 8 Prediabetic Overw/Obese Male Only	5 weeks	Ø	1. ↓*† 2. ↓	1. ↓*† 2. ↓	--	Ø	Ø	1. ↑ * 2. Ø
Carlson, O. et al. 2007 [33]	Crossover Trial	1. 1-Meal (4-h) 2. 3-Meal (4-h)	N= ? Healthy Male/Female	8 weeks	1. ↑ *† 2. Ø	Ø	--	--	1. ↑ *† 2. Ø	1. ↑ † 2. Ø	--
TRF 7-10 h											
Hutchison, A. T. et al. 2019 [27]	Cross Over Trial	1. TRFe (9h) 2. TRFd (9h)	N=15 Prediabetic Overw/Obese Male Only	1 week	1. ↓* 2. Ø	Ø	--	--	--	--	1. ↓* 2. ↓*
McAllister, M. J. et al. 2019 [10]	Randomized Trial	1. TRF(8h) ad lib. 2. TRF(8h) iso-cal.	N= 22 Healthy Male Only	4 weeks	Ø	1. ↑† 2. ↑	--	--	1. ↑† 2. ↑	--	Ø

*** Tinsley, G. M. et al. 2019** [11]	TRF	1. TRF (8h) 2. TRF (8h) + HMB 3. Control	N= 40 Healthy Active Female Only	8 weeks	Ø	Ø	--	--	Ø	Ø	Ø
*** Moro, T. et al. 2016** [9]	Randomized Trial	1. TRF (8h) 2. Control	N= 34 Healthy Active Male Only	8 weeks	1. ↓* 2. Ø	1. ↓* 2. Ø		--	Ø	1. ↑* 2. Ø	1. ↓*† 2. Ø
Kahleova, H. et al. 2014 [31]	Crossover Trial	1. TRF + 2 Meals 2. TRF + 6 Meals	N= 54 type 2 Diabetic Overw/Obese Male/Female	12 weeks	1. ↓*† 2. ↓*	1. ↓* 2. ↓*	--	Ø	1. ↑ * 2. Ø	Ø	1. ↓*† 2. ↓*
*** Kesztyus, D. et al. 2019** [28]	Longitudinal Trial	TRF (8-9 h)	N= 40 Overw/Obese Male/Female	12 weeks	--	--	--	↓*	Ø	Ø	Ø
*** Gabel, K. et al 2018** [7]	Randomized Trial	1. TRF (8h) 2. Control (Hist)	N= 23 Obese Male/Female	12 weeks	Ø	Ø	Ø	Ø	Ø	Ø	Ø
*** Wilkinson, M. J. et al. 2020** [8]	Longitudinal Trial	TRF (10h)	N= 19 Obese Metabolic Synd. Male/Female	12 weeks	Ø	Ø	Ø	Ø	↓*	Ø	Ø

∅: Non-significant change

* P < 0.05, Significantly different from baseline (within group effect).

† P < 0.05, Significantly different from the control or comparison group (between group effect). When control group present, only significant changes versus control reported.

Abbreviations: A1c: hemoglobin A1c, CRP: RCT: Randomized ontrolled trial, HDL: High density lipoprotein cholesterol, IR: Insulin resistance, LDL: Low density lipoprotein cholesterol, TG: Triglycerides, TRF: Time restricted feeding (prescribed eating window shown in parentheses), ADF: Alternate day fasting. CR: Caloric restriction.

Inflammatory Markers

The effects of ADF and TRF on inflammatory markers are reported in **Table 3.**

ADF

The effect of ADF on inflammatory cytokines and adipokines (i.e. IL-6, TNF-alpha, CRP, leptin, adiponectin) has only been measured in a handful of studies. Trepanowski et al. [34] compared ADF 25% with CR and Controls in participants with obesity for 24 weeks, showing a within group increase in IL-6. Harder-Laurissen et al [15] compared bed-rest-ADF versus bed-rest-controls in healthy males for 1 week, showing a within group decrease in IL-6. Five studies measured TNF-alpha. Johnson et al. [18] conducted a longitudinal trial with ADF 25% in obese male participants with asthma for 8 weeks, showing a significant reduction from baseline in TNF-alpha. However, Harder -Lauridssen et al. [15] showed a within group increase in TNF-alpha. In terms of leptin, three studies showed a within group decrease, but only Varady et al. [5] showed significantly greater reductions in leptin when comparing ADF 25% to controls in overweight participants for 12 weeks. Adiponectin (an anti-inflammatory adipokine) was measured only in the studies by Varady et al. [5] and Trepanowski et al. [34]. Both studies showed a within group increase, but not significantly greater than controls or CR. Finally, six studies measured CRP but only Varady et al. [5] showed a significantly greater increase in CRP when compared to controls. The other studies showed no effect on CRP. Taken together, the effects of ADF on markers of inflammation are not clear. We will need more studies measuring these parameters in order to draw definite conclusions about the effect of ADF on inflammation.

TRF

The effect of TRF on inflammatory markers has been tested in just a few recent studies. Two studies measured the effect of TRF in IL-6. Moro et al. [9] compared 8-h TRF with a control group in healthy active males for 8 weeks, showing a within group decrease in IL-6 and TNF-alpha compared to controls. Sutton et al. [32] compared early TRF with controls and showed no effect in IL-6 after 5 weeks. In terms of leptin, Moro et al. [9] was the only one to show significantly greater reductions in leptin when compared to controls. McAllister et al. [10] and Moro et al. [9] showed a within group increase in adiponectin but not significantly greater than controls. Finally, from the three studies that measured CRP, only McAllister et al. [10] showed a within group decrease but not significantly greater than isocaloric group. In sum, due to the paucity of data in this area, it is not possible to draw clear conclusions regarding the effects of TRF on inflammatory markers.

Summary: Metabolic Markers

The effects of ADF and TRF on parameters of metabolic health are still unclear due to the paucity of data in this area. Nevertheless, preliminary findings show that ADF appears to decrease fasting insulin and insulin resistance, but has little effect on fasting glucose or HbA1c. In comparison, TRF seems to induce significant reductions in fasting glucose, but not fasting insulin, insulin resistance and HbA1c. As for plasma lipids, ADF significantly reduces LDL cholesterol and triglycerides but does not affect HDL cholesterol. In contrast, TRF increases LDL cholesterol but has little effect on HDL and triglyceride levels. In terms of inflammatory markers, the available data is insufficient to draw clear conclusions.

Table 3 *The Effect of ADF and TRF on Inflammatory Markers*

Reference	Design	Intervention	Subjects	Length	IL-6	TNF-alpha	Leptin	Adiponectin	CRP
ADF (100% energy restriction on fast day)									
Stekovic, S. et al. 2019 [1]	RCT	1. ADF 2. Control	N= 57 Healthy Male/Female	4 weeks	--	--	--	--	Ø
* **Catenacci, V. A. et al. 2016** [14]	Randomized trial	1. ADF 2. CR	N= 26 Obese Male/Female	8 weeks + 24 weeks WM	--	--	1. ↓* 2. ↓*	--	--
ADF (25% energy restriction on fast day)									
***Harder-Lauridsen, N. M. et al 2017** [15]	Randomized Trial	1. ADF + Bed Rest 2. Bed rest (control)	N= 20 Healthy lean Male Only	1 week	1. ↓* 2. ↓*	1. ↑* 2. ↑*	--	--	--
Johnson, J. B. et al. 2007 [18]	Longitudinal Trial	ADF	N= 10 Asthma Obese Male/Female	8 weeks	--	↓*	Ø	--	Ø
Liu, B. et al. 2019 [35]	Randomized Trial	1. ADF 100 2. ADF 70 3. CR 70	N= 76 Overw/Obese Female	8 weeks	Ø	Ø	--	--	--
* **Varady, K. A.et al. 2013** [5]	RCT	1. ADF 2. Control	N= 32 Healthy/Overw Male/Female	12 weeks	--	--	1. ↓*† 2. Ø	1. ↑*† 2. Ø	1. ↑*† 2. Ø
* **Bhutani, S. et al. 2013** [3]	RCT	1. ADF + exercise 2. ADF 3. Exercise 4. Control	N= 64 Obese Male/female	12 weeks	--	--	--	--	Ø
* **Bowen, J. et al. 2018** [23]	Randomized trial	1. ADF HP + CR 2. CR+HP	N= 162 Obese Male/Female	16 weeks + 8 weeks WM	--	--	--	--	Ø
***Gabel, K. et al. 2019** [24]	RCT	1. ADF 2. CR 3. Control	N= 43 IR Obese Male/Female	24 weeks	Ø	Ø	--	--	Ø
***Trepanowski, J. F. et al. 2018** [34]	RCT	1. ADF 2. CR 3. Control	N= 100 Overw/Obese Male/Female	24 weeks	1.↑* 2.↑*	Ø	1. ↓* 2. ↓* 3. Ø	1. ↑* 2. ↑* 3. Ø	--
TRF 4-6 h									
***Sutton, E. F. et al. 2018** [32]	Crossover Trial	1. Early TRF (6h) 2. Control (12 h)	N= 8 Prediabetic Overw/Obese	5 weeks	Ø	--	Ø	Ø	Ø

			Male Only						
TRF 7-10 h									
***McAllister, M. J. et al. 2019** [10]	Randomized Trial	1. TRF (8h) ad lib 2. TRF (8h) iso-cal	N= 22 Healthy Male Only	4 weeks	--	--	--	1. ↑* 2. ↑*†	1. ↓ 2. ↓†
***Moro, T. et al. 2016** [9]	Randomized Trial	1. TRF (8h) 2. Control	N= 34 Healthy Active Male Only	8 weeks	1. ↓* 2. Ø	1. ↓* 2. Ø	1. ↓*† 2. Ø	1. ↑ * 2. Ø	--
***Wilkinson, M. J. et al. 2020** [8]	Longitudinal Trial	TRF (10h)	N= 19 Obese Met. Syndrome. Male/Female	12 weeks	--	--	--	--	Ø

∅: Non-significant change

* P < 0.05, Significantly different from baseline (within group effect).

† P < 0.05, Significantly different from the control or comparison group (between group effect). When control group present, only significant changes versus control reported.

Abbreviations: CRP: C reactive protein RCT: Randomized controlled trial, IL-6: Interleukin 6, TRF: Time restricted feeding (prescribed eating window shown in parentheses), ADF: Alternate day fasting. CR: Caloric restriction.

Sleep

Fasting and sleep may interact and impact the circadian rhythm of various body organs when food is not consumed at suitable time relative to the timing on the circadian clock. Thus, it is speculated that IF has the potential to improve sleep outcomes [36]. The effects of weight loss and IF on sleep are reviewed below.

Weight loss and sleep

Sleep quality and sleep duration are considered risk factors for the development of obesity and its complications. Only 35% of adults meet the recommended 7-9-h of sleep each night [37]. The direction of the causality is complex because obesity in itself is associated with poor sleep quality and shorter sleep duration [38-40]. Weight loss by means of dietary restriction may help improve sleep quality and quantity [41, 42]. The Pittsburgh Sleep Quality Index (PSQI) is often used to measure sleep quality, timing, and duration. A PSQI total score >5 indicates poor sleep quality. The questionnaire also asks for usual bedtime, usual wake time, and hours of actual obtained sleep [43]. Chauput et al [44] evaluated weight loss in obese men, and they reported significantly improved sleep quality with 5% weight loss. The CALERIE study [42] also reported a significant improvement in subjective sleep quality, sleep duration, and overall PSQI scores after 12% weight loss over a 52-week period. These changes did not remain significant at follow-up at 104 weeks [42]. The POWER-UP study [41] also evaluated the effect of weight loss on sleep quality and duration. This trial evaluated the same diet and activity prescription as CALEARIE but with usual care, brief lifestyle counseling, or enhanced lifestyle counseling. After 24 weeks, the mean minutes of sleep increased significantly in the group who lost ≥5% body weight. After 104 weeks, sleep duration was significantly different between the usual care participants and the

enhanced counseling participants, as usual care decreased sleep minutes and enhanced care increased sleep minutes. PSQI scores improved in all 3 groups by week 104; no between group differences were noted. PSQI scores also improved significantly in those that lost ≥5% after 24 weeks, however, at 104 weeks this was no longer significant [41]. Verhoef et al [45] reported significant improvements in daytime sleepiness and time to fall asleep during an 8-week VLCD weight-loss intervention. Short and average sleepers (≤ 9hrs) reported increased sleep duration, whereas long sleepers (≥ 9hrs) reported no change in sleep duration [45]. It appears that weight loss of at least 5% may improve sleep quality and duration in those with short to moderate sleep duration at baseline.

Fasting and sleep

Only a few studies have evaluated the effects of fasting on sleep outcomes. In a recent study by Wilkinson et al [8], 10-h TRF improved morning restfulness but had no effect on sleep quality after 12 weeks in subjects with metabolic syndrome. In another study of 10-h TRF by Gill and Panda [46], overweight participants experienced improved sleep quality after 16 weeks of intervention. In contrast, two other studies of TRF showed no effect on sleep parameters. Gabel et al [47] demonstrated no change in sleep quality or sleep duration after 12 weeks of 8-h TRF in subjects with obesity. Similarly, Hutchison et al [27] showed no effect of 9-h TRF on sleep duration in men with obesity. Almeneessier et al [36] did observe a change in the circadian pattern of melatonin during Ramadan fasting while controlling for caloric intake, energy expenditure, light exposure, and sleep schedule. In view of these equivocal findings, the effects of TRF on sleep still remain unclear.

Safety

The safety of ADF and TRF has been evaluated in several recent studies. This section summarizes the effect of ADF and TRF on general health (complete blood count), thyroid hormones, reproductive hormones, eating disorder symptoms, and frequency of adverse events.

Complete blood count

Complete blood count (CBC) is a blood test used to evaluate overall health and is frequently used in general medical practice. Stote et al. [48] evaluated the effect of TRF on CBC. They showed that reducing meal frequency to one 4-h window daily did not change CBC in normal-weight adult subjects. Gabel et al. [49] also showed that CBC remained unchanged after 12 weeks of 8-h TRF. These preliminary findings suggest that intermittent fasting does not alter CBC in healthy individuals.

Thyroid hormones

Some studies have assessed changes in thyroid hormones during IF. Moro et al. [9] studied the effect of 8 weeks of 8-h TRF with resistance training in young male athletes. The study showed that plasma T3 decreased slightly, but TSH remained unchanged. Unfortunately, T4 was not measured in this study, so it is difficult to assess if the ratio of T3:T4 changed with TRF. Akasheh et al [50] analyzed the effects of 24 weeks of ADF on thyroid hormone levels in participants with obesity and subclinical hypothyroidism relative to a daily CR group. The results show that free T4, T3 and TSH remained unchanged despite an 8% weight loss in both groups. The authors mention that T3 levels during IF may be slightly lower in

lean individuals versus subjects with obesity and subclinical hypothyroidism. These preliminary findings suggest that fasting does not induce severe alterations of thyroid hormones.

Reproductive hormones

The effect of IF on reproductive hormones have been studied in a handful of trials. Harvie et al [51] analyzed the effect of 24 weeks of fasting two days per week on testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone-sulfate (DHEAS), androstenedione or prolactin in premenopausal woman. Results show that this fasting regimen did not alter any of these reproductive parameters. In contrast, Moro et al [9] showed that 8 weeks of 8-h TRF decreased free and total testosterone in young male athletes. However, these decreases in anabolic hormones (testosterone) did not induce adverse changes in body composition or muscular strength. These findings suggest that IF does not induce severe alterations in reproductive hormones. However, the effect of IF on male and female fertility is currently unknown, as no studies have tested the effects of these diets on the ability to conceive. More long-term studies analyzing the effect of fasting on reproductive hormones, fertility markers and in polycystic ovary syndrome are needed.

Eating disorder symptoms

IF has been criticized for potentially increasing the risk for eating disorders. A few studies have examined how IF impacts eating disorder parameters. For instance, Gabel et al [49] examined the effect of 12 weeks of 8-h TRF on eating disorder symptoms. The results showed that the risk for depression, binge eating, purgative behavior, fear of fatness, restrictive eating and avoidance of

forbidden foods did not change from baseline to week 12. In addition, Hoddy et al [52] demonstrated that body image perception improved after 8 weeks of ADF, showing possible favorable effects of ADF on eating disorder risk. These results are in accordance with those studies analyzing the effect of caloric restriction on eating disorder risk. The CALERIE trial [53] [54] showed that 25% caloric restriction did not induce eating disorders or adverse psychological effects. From these preliminary findings we can speculate that IF does not increase the risk for disordered eating. However, it is important to mention that most fasting studies exclude participants with a history of eating disorders. Thus, these results can be extrapolated only for people with no history of eating disorders.

Gastrointestinal and neurological adverse effects

Frequency of adverse events during periods of fasting are routinely monitored in clinical trials. Hoddy et al. [52] examined the safety of an 8-week ADF protocol and found little or no disturbances in terms of constipation, or diarrhea. Sutton et al. [32] analyzed the safety of a 6-h early TRF in men with prediabetes and showed no serious adverse events, besides very minor gastrointestinal issues. Gabel et al. [49] assessed the safety of 12 weeks of 8-h TRF in adults with obesity and showed no change in terms of gastrointestinal and neurological symptoms over the course of the study. Wilkinson et al. [8] studied the impact of a 10-h TRF for 12 weeks and reported no gastrointestinal adverse events. Likewise, Sundfor et al. [55] assessed the safety of 24 weeks of intermittent energy restriction and reported no serious adverse events, besides mild symptoms such as headaches during the initial phase of the study. In conclusion, findings to date show that IF produces little or no prolonged adverse events.

General Conclusion for Literature Review

This review summarized the effects of ADF and TRF on body weight, body composition, metabolic disease risk factors, inflammatory markers, sleep, and safety. ADF and TRF are both effective weight loss strategies in adults with obesity, but ADF appears to produce greater weight loss (3-7%) versus TRF (2-3%) after short intervention periods (8-12 weeks). In terms of body composition, both ADF and TRF produce significant fat mass reductions, but ADF produces a more pronounced fat mass loss. Neither diet has any substantial effect on fat free mass or visceral fat mass. With regards to glucoregulatory factors, ADF significantly decreased fasting insulin and insulin resistance, but had no effect on fasting glucose or HbA1c. In comparison, TRF seems to induce significant reductions in fasting glucose, but not fasting insulin, insulin resistance and HbA1c. As for plasma lipids, ADF significantly reduces LDL cholesterol and triglycerides but does not affect HDL cholesterol. In contrast, TRF increases LDL cholesterol but has little effect on HDL and triglyceride levels. In terms of inflammatory markers, the available data is insufficient to draw clear conclusions about the efficacy of these two fasting approaches. Both diets appear to safe, and produce little or no adverse effects in terms of gastrointestinal issues, neurological issues, hormonal disturbances, or eating disorder symptoms. The effects of fasting on sleep is still unclear, as very few studies have been performed in this area. In summary, the two main forms of IF (ADF and TRF) are safe and effective diet therapies for weight loss in adults with obesity. These fasting regimens also produce some improvements in metabolic health, but much more research will be needed to clarify if these effects persist long-term.

III. MANUSCRIPT 1

The effect of four-hour and six-hour time restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity

Published in Cell Metabolism. 2020;32(3):366-378.

Sofia Cienfuegos, Kelsey Gabel, Faiza Kalam, Mark Ezpeleta, Eric Wiseman, Vasiliki Pavlou, Shuhao Lin, Manoela Lima Oliveira, Krista A. Varady

Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL

Correspondence and reprint requests:

Krista Varady, PhD, Professor of Nutrition

Department of Kinesiology and Nutrition, University of Illinois at Chicago

1919 West Taylor Street, Room 532, Chicago, IL, 60612

Tel: 312-996-7897, Email: varady@uic.edu

Funding: National Institutes of Health, NIDDK, R01DK119783

Trial registration: Clinicaltrials.gov NCT03867773

Summary

Time restricted feeding (TRF) is a form of intermittent fasting that involves confining the period of eating to 4-10 h and water fasting for the rest of the day. Although these diets have grown in popularity, very few studies have examined their weight loss efficacy. We conducted the first human trial to compare the effects of two popular forms of TRF (4-h and 6-h) on body weight and cardiometabolic risk indicators. Adults with obesity were randomized to 4-h TRF (eating only between 3 to 7 pm, fasting between 7 to 3 pm), 6-h TRF (eating only between 1 to 7 pm, fasting between 7 to 1 pm), or a control group (no meal timing restrictions) for 8 weeks. Subjects in the TRF groups were not required to monitor energy intake during their eating windows. After 8 weeks, weight loss was not significantly different between the 4-h TRF group (-3.2 $\pm$ 0.4%) and 6-h TRF group (-3.2 $\pm$ 0.4%), but both groups differed ($P < 0.001$) from controls. Energy intake was reduced by 4-h TRF (-528 $\pm$ 102 kcal/d, -2209 $\pm$ 427 kJ/d) and 6-h TRF (-566 $\pm$ 142 kcal/d, -2368 $\pm$ 594 kJ/d) by week 8, versus controls, without calorie counting. Reductions in insulin resistance, blood pressure, and oxidative stress were observed with 4-h and 6-h TRF, relative to controls, with no difference between intervention groups. These findings suggest that both 4-h and 6-h TRF induce mild reductions in body weight over 8 weeks (~3%) and show promise as interventions for weight loss. These diets may also improve some aspects of cardiometabolic health.

Key words: Time restricted feeding, intermittent fasting, body weight, insulin resistance, blood pressure, adults with obesity

Introduction

Intermittent fasting has greatly increased in popularity over the past few years owing to its ability to produce clinically significant weight loss and confer protection against metabolic disease [56, 57]. Intermittent fasting is an umbrella term for three different types of diets: alternate day fasting, the 5:2 diet, and time restricted feeding (TRF). Alternate day fasting involves a "fast day", where energy is severely restricted (e.g. 0-800 kcal/0-3350 kJ consumed), alternated with an ad libitum intake "feast day". The 5:2 diet, is a modified version of alternate day fasting, and includes only two fast days per week followed by five ad libitum feast days. TRF, on the other hand, differs from these two other approaches in that it involves deliberately restricting the times during which energy is ingested. This diet involves confining the eating window to a specified number of hours per day and fasting (with zero-calorie beverages) for the remaining hours of the day. During the eating window, individuals are not required to count calories or monitor food intake in any way. Some of the most popular forms of TRF followed by the general public are 4-h TRF (a.k.a. The Warrior Diet) and 6-h TRF. Despite their growing popularity, no trial to date has examined whether these regimens are effective for producing clinically significant weight loss.

The effects of alternate day fasting and the 5:2 diet on metabolic disease risk have been studied in dozens of human trials to date. Accumulating evidence suggests that alternate day fasting produces 5-7% weight loss over short durations (<6 months) [3-5, 14, 18-20, 22, 23, 58, 59]. Alternate day fasting also produces several cardiometabolic benefits, such as reducing blood pressure, LDL cholesterol levels, triglycerides, fasting insulin, insulin resistance, inflammation and oxidative stress [3-5, 12, 14, 18-20, 22, 23, 58, 59]. As for the 5:2 diet, findings from human trials suggest that this regimen

produces very similar reductions in body weight and metabolic disease risk parameters as alternate day fasting [51, 55, 60, 61].

The effects of TRF have been studied much less extensively. To date, only six human trials of TRF have been performed [7-9, 11, 32, 62], and only three of these have examined the effects of this diet on weight loss [7, 8, 62]. Initially, a single-arm 16-week study of 10-h TRF demonstrated that adults with overweight lost 3.6% of body weight and reduced energy intake by ~20%, without calorie counting [62]. The next study examined the weight loss efficacy of 8-h TRF [7]. After 12 weeks, adults with obesity lost 2.6% of body weight and reduced energy intake by ~20% from baseline. Most recently, another single-arm trial of 10-h TRF demonstrated 3.0% weight loss and an 8% reduction in caloric intake after 12 weeks in participants with metabolic syndrome [8]. Each of these studies report excellent compliance with the prescribed eating windows, i.e. subjects ate within their prescribed eating windows 80-90% of the time over 12-16 weeks.

In addition to weight loss, TRF may also benefit cardiometabolic health. After 8-weeks of 8-h TRF, pronounced reductions in fasting glucose, insulin and insulin resistance were observed [9]. Improvements in insulin sensitivity and beta-cell function were also demonstrated when food intake was limited to a 6-h window in men with pre-diabetes [32]. Blood pressure is regularly decreased with this diet, [7, 8], even in the absence weight loss [32]. The effects of TRF on plasma lipids levels, however, is less clear. While some studies show improvements in triglycerides [9] and LDL cholesterol levels [8], most report no effect on any lipid parameter [7, 11, 32].

Whether TRF exerts its metabolic benefits by improving markers of oxidative stress and inflammation, is an important question that remains unresolved. The effects of TRF on oxidative stress have only been evaluated in one human trial to date [32]. After 5 weeks, early 6-h TRF (i.e. eating all food before 3 pm in a 6-h window) lowered 8-isoprostane levels (a marker of oxidative stress to lipids) by 14% [32]. As for inflammatory markers, the limited data available suggests that TRF has no effect on circulating TNF-alpha and IL-6 in human subjects [9, 32].

Very few adverse events have been reported during TRF. After 12 weeks of 8-h or 10-h TRF, occurrences of nausea, constipation, diarrhea, headaches, fatigue, and irritability did not change from baseline to post-treatment [8, 63]. Complete blood count and disordered eating behaviors were also unaltered after 12 weeks of 8-h TRF [63]. In contrast, early 6-h TRF resulted in a few minor cases of vomiting, headaches, increased thirst and diarrhea [32]. When 8-h TRF was combined with resistance training, reductions in the thyroid hormone, total triiodothyronine (T3), slightly below the normal level, were reported [9]. As for sleep, no negative effects on sleep quantity or quality have been observed with either 8-h or 10-h regimens [62, 64].

Whether the timing of the eating window (early versus late) during TRF impacts weight loss and metabolic disease risk is still largely unknown due to the paucity of data in this area. Accumulating evidence suggests that the body is optimized for food intake in the morning [65-67]. That is, insulin sensitivity, beta-cell responsiveness and thermic effect of food are all higher in the morning than in the afternoon or evening [65-67]. As such, it has been postulated that earlier eating windows during TRF may produce superior metabolic benefits than later eating windows. In a recent study [32], insulin

sensitivity and beta-cell function were improved by early 6-h TRF (eating all food before 3 pm) when compared to controls (eating all food between 7 am to 7 pm). While the results of this highly controlled trial are valuable to the field, this study is limited in that it did not directly compare the effects of early versus late TRF. The effect of meal timing on body weight and glycemic control has also been evaluated in human trials of breakfast skipping. While some studies suggest that skipping breakfast (fasting until 11 am) has negative effects on weight management and glycemic control [68-70], others show no deleterious effects on these parameters [71-73]. Thus, whether extended morning fasts negatively impact body weight and glucose homeostasis is still unclear. In designing a TRF intervention, it is also important to consider the social aspects of eating. The majority of social eating and drinking events occur in the evening (e.g. eating dinner with one's family). Allowing participants to continue to engage in their habitual social eating patterns could play an important role in diet adherence and tolerability [74]. In the present study, we chose to shift the eating window to the afternoon/evening as later eating occasions allow individuals to engage in more family meals/social eating, which may improve overall compliance.

This study is the first randomized controlled trial to compare the weight loss efficacy of 4-h versus 6-h TRF in adults with obesity. The specific objective of this trial was to evaluate the impact of 4-h TRF (ad libitum intake from 3 to 7 pm) versus 6-h TRF (ad libitum intake from 1 to 7 pm) on body weight and metabolic disease risk parameters, versus a control group that had no meal timing restrictions. Compliance with the diets and occurrence of adverse events was also examined. We hypothesized that the 4-h TRF group would produce greater weight loss, when compared to the 6-h TRF group and controls. We also hypothesized that the 4-h group would yield greater blood pressure reductions,

better glycemic control, and more pronounced improvements in oxidative stress, due to larger decreases in body weight.

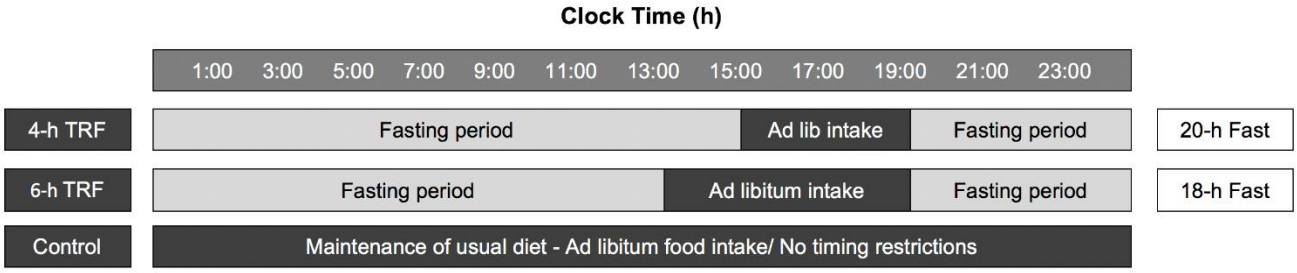


Figure 1. Time Restricted Feeding Interventions

During the 8-week intervention period, the 4-h TRF group ate ad libitum from 3:00-7:00 pm daily (20-h fast). The 6-h TRF group ate ad libitum from 1:00-7:00 pm daily (18-h fast). During the feeding window, there were no restrictions on types or quantities of foods consumed and participants were not required to monitor caloric intake. Controls were instructed to continue their usual diet pattern and did not have any meal timing restrictions.

Results and discussion

We conducted a 10-week randomized parallel-arm trial to compare the effects of 4-h and 6-h TRF versus controls on body weight in adults with obesity. Participants were randomized by a stratified random sample (based on age, sex, and BMI) into 1 of 3 groups: 4-h TRF, 6-h TRF, or a no-intervention control group. Briefly, the trial consisted of a 2-week baseline weight stabilization period followed by an 8-week TRF intervention period. During the 8-week intervention, the 4-h TRF group was instructed to eat ad libitum from 3 to 7 pm daily, and fast from 7 to 3 pm (20-h fast) (**Figure 1**). The 6-h TRF group was instructed to eat ad libitum from 1 to 7 pm daily, and fast from 7 to 1 pm (18-h fast). During the feeding windows, TRF participants were not required to monitor caloric intake and there were no restrictions on types or quantities of foods consumed. During the fasting window, TRF participants were encouraged to drink plenty of water and were permitted to consume energy-free beverages, such as black tea, coffee, and diet sodas. Controls were instructed to maintain their weight throughout the trial, and not to change their eating or physical activity habits. Controls visited the research center at the same frequency as the intervention groups for clinical measurements. The primary outcome measure was change in body weight. Secondary outcome measures were insulin resistance, blood pressure, plasma lipids, inflammatory cytokines, oxidative stress, and diet adherence.

Participants

As shown in **Figure 2**, 82 individuals expressed interest in the study. Of these participants, 24 were excluded as they did not meet one or more inclusion criteria. A total of 58 participants were randomized into the 4-h TRF group (n =19), 6-h TRF group (n = 20), or the control group (n = 19). At the conclusion of the 10-week trial, there were 16 completers in the 4-h TRF group, 19 completers in the 6-h TRF group, and 14 completers in the control group. The main reason for participant attrition was

scheduling conflicts. Notably, no one dropped out of the study due to dislike of the TRF intervention. Participants who completed the study were primarily middle-age, women with obesity who were normotensive and normocholesterolemic but insulin resistant (defined as HOMA-IR $\geq$ 2.7 [75, 76]) (**Table 1**). Baseline characteristics of the dropouts were comparable to those participants who completed the study.

4-h TRF does not produce superior changes in body weight compared to 6-h TRF

As shown in **Figure 3A**, weight loss by week 8 in the 4-h TRF group (Δ = -3.2 $\pm$ 0.4%) and 6-h TRF group (Δ = -3.2 $\pm$ 0.4%), was significantly different (P < 0.001) versus controls (0.1 $\pm$ 0.4%), with no significant differences between intervention groups. Compliance with the TRF interventions was excellent (**Figure 3B**). On average, participants in the 4-h TRF and 6-h TRF group reported being compliant with their feeding window on 6.2 $\pm$ 0.2 d/week and 6.2 $\pm$ 0.1 d/week, respectively, and this level of adherence did not change over the course of the trial (P = 0.76). Thus, 4-h TRF does not produce superior changes in body weight compared to 6-h TRF. Very few studies have examined the weight loss efficacy of TRF in individuals with obesity [7, 8, 62]. In a recent trial of 8-h TRF, body weight was reduced by 2.6% after 12 weeks in men and women with obesity [7]. Likewise, 10-h TRF produced 3.6% weight loss after 16 weeks [62] and 3.0% weight loss after 12 weeks [8]. To our knowledge, no other study has examined the effect of 4-h or 6-h TRF as a weight loss regimen, thus, there is no data to which to compare our findings. In comparison with other forms of intermittent fasting, the degree of weight loss achieved with 4-h and 6-h TRF may be on par with that observed during short-term alternate day fasting [3-5, 13, 14, 59] and the 5:2 diet [51, 55, 61].

At baseline (pre-intervention), the average fasting window was not significantly different (P = 0.55) between the 4-h TRF (10.8 $\pm$ 0.5 h) and 6-h TRF (10.3 $\pm$ 0.6 h) group. However, the duration of the baseline fasting window varied vastly between individual participants. For instance, in the 4-h TRF group, baseline fasting window ranged from 10 to 16 h/d. While in the 6-h TRF group, baseline fasting window ranged from 9 to 19 h/d. As such, we were interested in seeing if participants who experienced the greatest increase in their fasting windows, would lose the greatest amount of weight. Results reveal (**Figure 3C and 3D**) that greater extensions in fasting were not related to weight loss in either the 4-h TRF (r = -0.06, P = 0.86) or 6-h TRF group (r = -0.09, P = 0.76). Thus, baseline eating patterns may not predict weight loss success with TRF.

Fat mass change by week 8 in the 4-h TRF group (Δ = -2.8 $\pm$ 0.4 kg) and 6-h TRF group (Δ = -1.4 $\pm$ 0.3 kg), was significantly different (P < 0.001) versus controls (Δ = -0.6 $\pm$ 0.4 kg), with no significant differences between intervention groups (**Figure 4A**). Lean mass change by week 8 in the 6-h TRF group (Δ = -1.5 $\pm$ 0.2 kg) was significantly different (P = 0.01) versus the 4-h TRF group (Δ = -0.8 $\pm$ 0.4 kg) and controls (Δ = -0.3 $\pm$ 0.2 kg) (**Figure 4B**). Visceral fat mass change by week 8 in the 4-h TRF group (Δ = -0.18 $\pm$ 0.07 kg) was significantly different (P = 0.03) versus the 6-h TRF group (Δ = -0.14 $\pm$ 0.06 kg) and controls (Δ = -0.02 $\pm$ 0.05 kg) (**Figure 4C**).

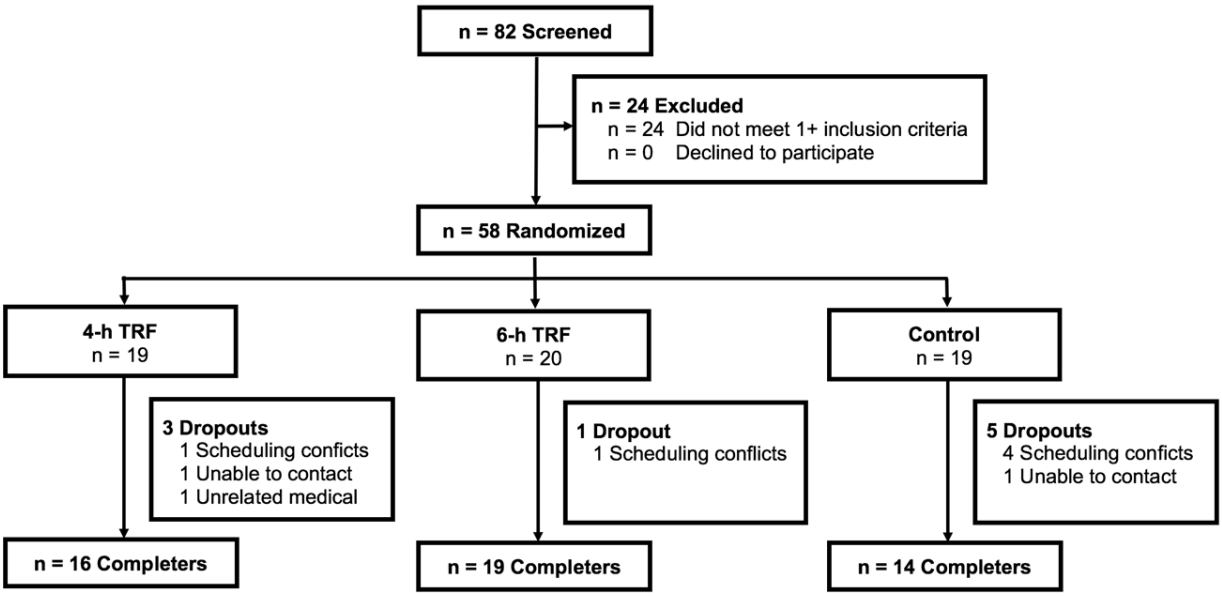


Figure 2. CONSORT diagram showing participant flow through the trial

A total of 82 individuals were screened and 24 were excluded as they did not meet one or more inclusion criteria. 58 participants were randomized into 1 of 3 groups: 4-h TRF, 6-h TRF, or control. At the conclusion of the 8-week intervention period, there were 16 completers in the 4-h TRF group, 19 completers in the 6-h TRF group, and 14 completers in the control group.

4-h and 6-h TRF produce similar reductions in fasting insulin and insulin resistance

Change in fasting glucose by week 8 was not significantly different (P = 0.18) between the 4-h TRF (Δ = -5.0 $\pm$ 3.8 mg/dl), 6-h TRF (Δ = -2.3 $\pm$ 2.0 mg/dl), or control groups (Δ = 2.6 $\pm$ 2.6 mg/dl) (**Figure 4D**). Change in fasting insulin by week 8 in the 4-h TRF group (Δ = -2.3 $\pm$ 1.5 µIU/mL) and 6-h TRF group (Δ = -1.9 $\pm$ 1.1 µIU/mL), was significantly different (P = 0.008) versus controls (Δ = 3.5 $\pm$ 1.4 µIU/mL), with no significant differences between intervention groups (**Figure 4E**). Likewise, change in insulin resistance by week 8 in the 4-h TRF group (Δ = -0.8 $\pm$ 0.4) and 6-h TRF group (Δ = -0.5 $\pm$ 0.3), was significantly different (P = 0.009) versus controls (Δ = 1.0 $\pm$ 0.4), with no significant differences between intervention groups (**Figure 4F**). Change in circulating HbA1c by week 8 was not significantly

different (P = 0.59) between the 4-h TRF (Δ = -0.2 $\pm$ 0.1%), 6-h TRF (Δ = -0.2 $\pm$ 0.1%), or control groups (Δ = -0.1 $\pm$ 0.1%) (data not shown).

This trial is the first to compare the effects of 4-h versus 6-h TRF on glucoregulatory factors. No change in glucose was noted, which is similar to what has been reported previously by other intermittent fasting studies [12, 24, 32, 51, 60, 77]. In contrast, insulin and insulin resistance are routinely improved by TRF, alternate day fasting, and 5:2 [12, 24, 32, 51, 60, 77]. TRF has also been shown to improve beta-cell responsiveness in participants with prediabetes [32]. More recently, it was shown that intermittent fasting lowered insulin resistance *twice* as much as daily calorie restriction (CR), despite similar weight loss between the two intervention groups [24]. It should be noted, however, that the reductions in insulin and insulin resistance noted here are partly driven by a worsening in the control arm. It is questionable whether these improvements by TRF would have been noted in the absence of this. Our results are also limited in that we measured these glucoregulatory parameters only in the morning. Insulin sensitivity and glucose tolerance peak shortly after waking [65]. As such, future studies should measure these endpoints over a 24-h period (instead of the morning only) to see these regimens truly only impact insulin and insulin resistance, without concomitant changes in glucose. One proposed mechanism by which fasting may improve glycemic control involves the metabolic switch. The metabolic switch, which occurs when changing from fed to fasted state, induces hepatocyte production of ketone bodies, increasing insulin sensitivity and decreasing fat accumulation. Insulin sensitivity of muscle cells is also enhanced in response to the metabolic switch [56].

Another outstanding question in the field is whether the metabolic benefits of intermittent fasting are due to *fasting* (long periods of food abstention during the day) or merely just weight loss. To see whether fasting has benefits independent of weight loss, some TRF studies have required subjects to stay weight stable by consuming weight maintenance energy needs. In a 6-h TRF trial, several metabolic indicators, including insulin sensitivity, beta-cell responsiveness, and oxidative stress improved after 5 weeks, despite no weight loss [32]. Contrary to these findings, two other studies show impaired glucose tolerance in conjunction with elevations in LDL cholesterol and blood pressure when subjects consumed all of their energy needs in a single meal over a 8-week period [33, 78]. Since the data in this area is still limited it is difficult to draw meaningful conclusions. Nevertheless, these preliminary findings may suggest that fasting produces metabolic benefits independent of weight loss, just as long as subjects are not required to gorge (consume all their energy needs for the day) within a 1-h time frame. It is apparent that much more research will be needed before solid conclusions can be reached.

Table 4 Baseline Characteristics

Characteristic	Completers			Dropouts		
	4-h TRF	6-h TRF	Control	4-h TRF	6-h TRF	Control
n	16	19	14	3	1	5
Age (y)	49 ± 2	46 ± 3	45 ± 2	41 ± 8	62 ± 0	47 ± 4
Sex						
Female	14 (88%)	18 (95%)	12 (86%)	3 (100%)	1 (100%)	5 (100%)
Male	2 (12%)	1 (5%)	2 (14%)	0 (0%)	0 (0%)	0 (0%)
Race or ethnic group						
White	1 (6%)	3 (16%)	2 (14%)	0 (0%)	0 (0%)	0 (0%)
Black	12 (75%)	12 (63%)	6 (43%)	2 (67%)	1 (100%)	4 (80%)
Asian	0 (0%)	3 (16%)	2 (14%)	0 (0%)	0 (0%)	0 (0%)
Hispanic	2 (13%)	1 (5%)	4 (29%)	1 (33%)	0 (0%)	1 (20%)
Other	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Body weight and composition						
Body weight (kg)	101 ± 5	99 ± 5	93 ± 5	92 ± 5	92 ± 0	97 ± 4
Fat mass (kg)	48 ± 3	48 ± 3	43 ± 3	--	--	--
Lean mass (kg)	52 ± 2	50 ± 3	48 ± 3	--	--	--
Visceral fat mass (kg)	1.4 ± 0.2	1.3 ± 0.1	1.1 ± 0.2	--	--	--
Height (cm)	167 ± 2	163 ± 2	160 ± 2	159 ± 2	152 ± 0	160 ± 3
Body-mass index (kg/m^2)	36 ± 1	37 ± 1	36 ± 1	37 ± 3	40 ± 0	38 ± 2
Glucoregulatory factors						
Fasting glucose (mg/dl)	88 ± 2	94 ± 2	96 ± 5	87 ± 0	87 ± 0	95 ± 5
Fasting insulin (μIU/mL)	12 ± 2	16 ± 3	12 ± 2	13 ± 0	23 ± 0	15 ± 6
Insulin resistance (HOMA-IR)	2.7 ± 0.4	3.7 ± 0.8	2.9 ± 0.4	2.7 ± 0	4.9 ± 0	3.6 ± 1.2
HbA1c (%)	5.9 ± 0.2	5.9 ± 0.1	5.9 ± 0.2	6.0 ± 0	5.4 ± 0	6.2 ± 0.5
Blood pressure and heart rate						
Systolic blood pressure (mm Hg)	135 ± 5	128 ± 4	122 ± 5	124 ± 0	153 ± 0	150 ± 23

Diastolic blood pressure (mm Hg)	88 ± 2	84 ± 2	81 ± 3	82 ± 0	98 ± 0	94 ± 9
Heart rate (bpm)	73 ± 2	68 ± 2	70 ± 3	72 ± 0	66 ± 0	70 ± 9
Plasma lipids						
LDL cholesterol (mg/dl)	95 ± 6	104 ± 8	108 ± 6	104 ± 0	143 ± 0	96 ± 18
HDL cholesterol (mg/dl)	57 ± 5	54 ± 3	56 ± 4	49 ± 0	52 ± 0	63 ± 10
Triglycerides (mg/dl)	91 ± 11	95 ± 7	84 ± 11	110 ± 0	76 ± 0	94 ± 27
Inflammation and oxidative stress						
TNF-alpha (pg/ml)	8.3 ± 1.7	14.2 ± 2.7	11.9 ± 2.6	--	--	--
IL-6 (pg/ml)	2.4 ± 0.7	5.2 ± 1.6	4.5 ± 1.3	--	--	--
8-isoprostane (pg/ml)	34.1 ± 4.6	33.8 ± 3.6	32.6 ± 4.8	--	--	--

Values are expressed as mean ± SEM. HOMA-IR: Homeostasis Model Assessment-Insulin resistance. -- Data not available.

Dropout data: All dropouts occurred during week 1 or 2 of the study. Baseline body weight, height and BMI was collected for all dropouts. None of the dropouts attended the baseline DXA scan visit, so no body composition data are available for these participants. Only a few dropouts attended the baseline blood draw/blood pressure visit (4-h TRF: n = 1, 6-h TRF: n = 1, Control: n = 3), so only data for these subjects are included here. TNF-alpha, IL-6, and 8-isoprostane data are not available for dropouts as not enough blood could be collected from these participants.

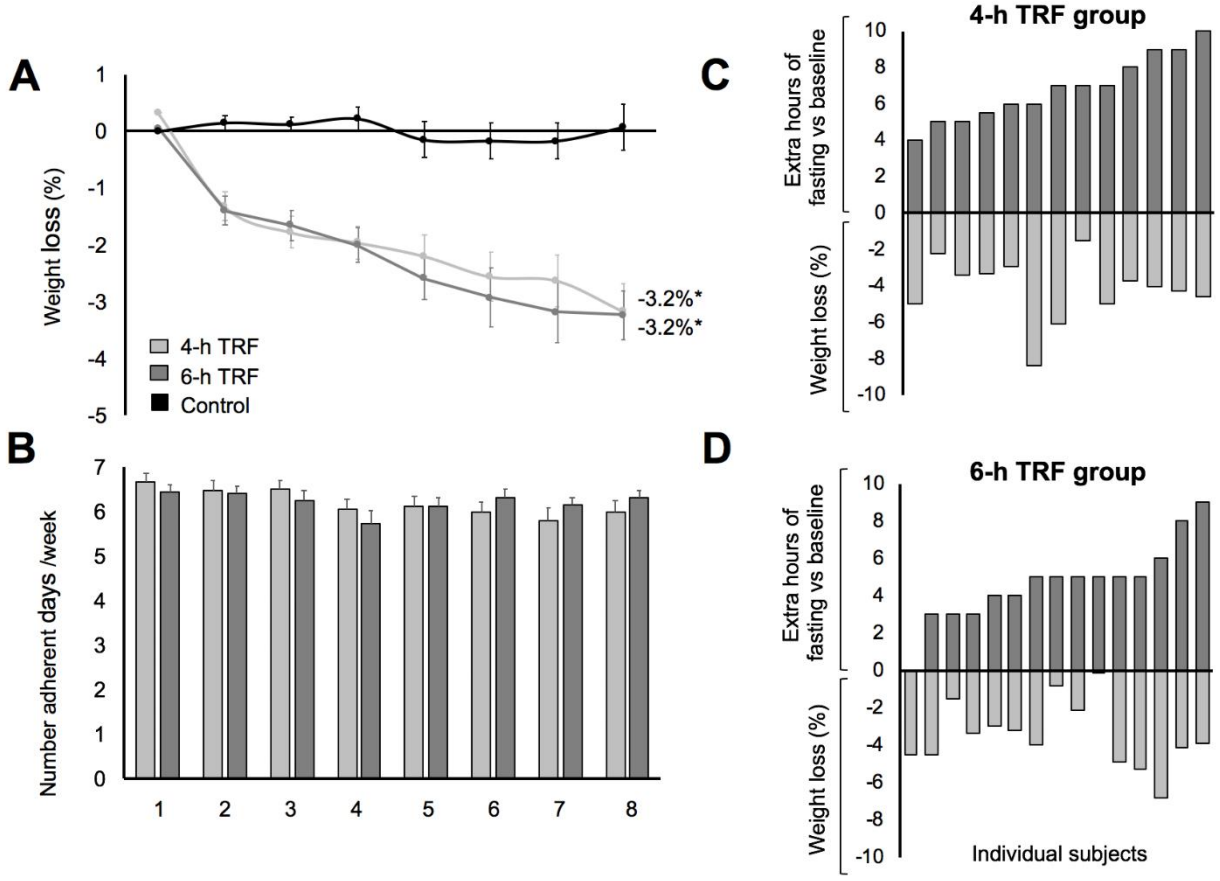


Figure 3. Weight loss and diet compliance

After 8 weeks, weight loss was not significantly different between the 4-h TRF and 6-h TRF group, but both groups differed from controls **(A)**. Subjects in the 4-h and 6-h TRF groups were highly compliant with their prescribed eating windows at each week of the study **(B)**. The

extent to which the fasting window increased from baseline was not related to degree of weight loss in the 4-h TRF group **(C)** or 6-h TRF group **(D)**. Values presented as mean ± SEM.

*Change score (baseline to week 8) significantly different from controls (P < 0.001, ANOVA).

4-h and 6-h TRF produce similar improvements in blood pressure but do not affect LDL cholesterol, HDL cholesterol or triglycerides

Change in systolic blood pressure by week 8 in the 4-h TRF group (Δ = -5.0 ± 2.2 mm Hg) was significantly different (P = 0.03) versus the 6-h TRF group (Δ = -4.4 ± 2.3 mm Hg) and controls (Δ = -3.7 ± 2.8 mm Hg) (**Figure 4G**). Change in diastolic blood pressure by week 8 in the 6-h TRF group (Δ = -3.2 ± 1.5 mm Hg) was significantly different (P = 0.04) versus the 4-h TRF group (Δ = -2.8 ± 1.0 mm Hg) and controls (Δ = 2.4 ± 2.2 mm Hg) (**Figure 4H**). Change in heart rate by week 8 was not significantly different (P = 0.46) between the 4-h TRF (Δ = -2.8 ± 1.7 bpm), 6-h TRF (Δ = 0.6 ± 2.0 bpm), or control groups (Δ = -1.6 ± 2.0 bpm) (**Figure 4I**). These reductions in blood pressure are on par with what has been reported previously during short-term intermittent fasting. For instance, after 2-3 months of alternate day fasting or the 5:2 diet, systolic blood pressure is typically lowered by 5-8 mm Hg, while diastolic blood pressure is reduced by 3-5 mm Hg [19, 20, 23, 51, 58]. As for TRF, 6-h early TRF produced dramatic decreases in both systolic and diastolic blood pressure (-10-11 mm Hg) [32], while 8-h TRF has been shown to reduce systolic blood pressure (-7 mm Hg) [7], but not always [11]. It has been proposed that elevated circulating insulin may increase blood pressure [79, 80]. Thus, it's possible that the reductions in blood pressure noted here may be partly driven by decreases in insulin.

Neither intervention had any effect on plasma lipid levels. For example, change in LDL cholesterol by week 8 was not significantly different (P = 0.44) between the 4-h TRF (Δ = 2.6 ± 5.7 mg/dl), 6-h TRF (Δ =

-4.8 ± 5.1 mg/dl), or control groups (Δ = -2.0 ± 3.7 mg/dl) (**Figure 4J**). Likewise, change in HDL cholesterol by week 8 was not significantly different (P = 0.96) between the 4-h TRF (Δ = -2.4 ± 1.3 mg/dl), 6-h TRF (Δ = -0.8 ± 1.4 mg/dl), or control groups (Δ = -0.7 ± 1.0 mg/dl) (**Figure 4K**). Change in triglycerides by week 8 was not significantly different (P = 0.95) between the 4-h TRF (Δ = -1.9 ± 6.7 mg/dl), 6-h TRF (Δ = 2.6 ± 4.6 mg/dl), or control group (Δ = 4.5 ± 3.2 mg/dl) (**Figure 4L**). The effects of intermittent fasting on plasma lipids are highly variable. While some studies report decreases in triglycerides and LDL cholesterol [18, 19, 23, 51], most show no effect on these lipid parameters [3, 7, 9, 20, 32, 58]. HDL also generally remains unaffected by these diets, though one study observed minor increases [4]. It should be noted, however, that the participants in the present study (and most previous studies) were not hypercholesterolemic. Since their baseline levels of LDL cholesterol and triglycerides were already in the normal range, it is not surprising that further reductions were not observed.

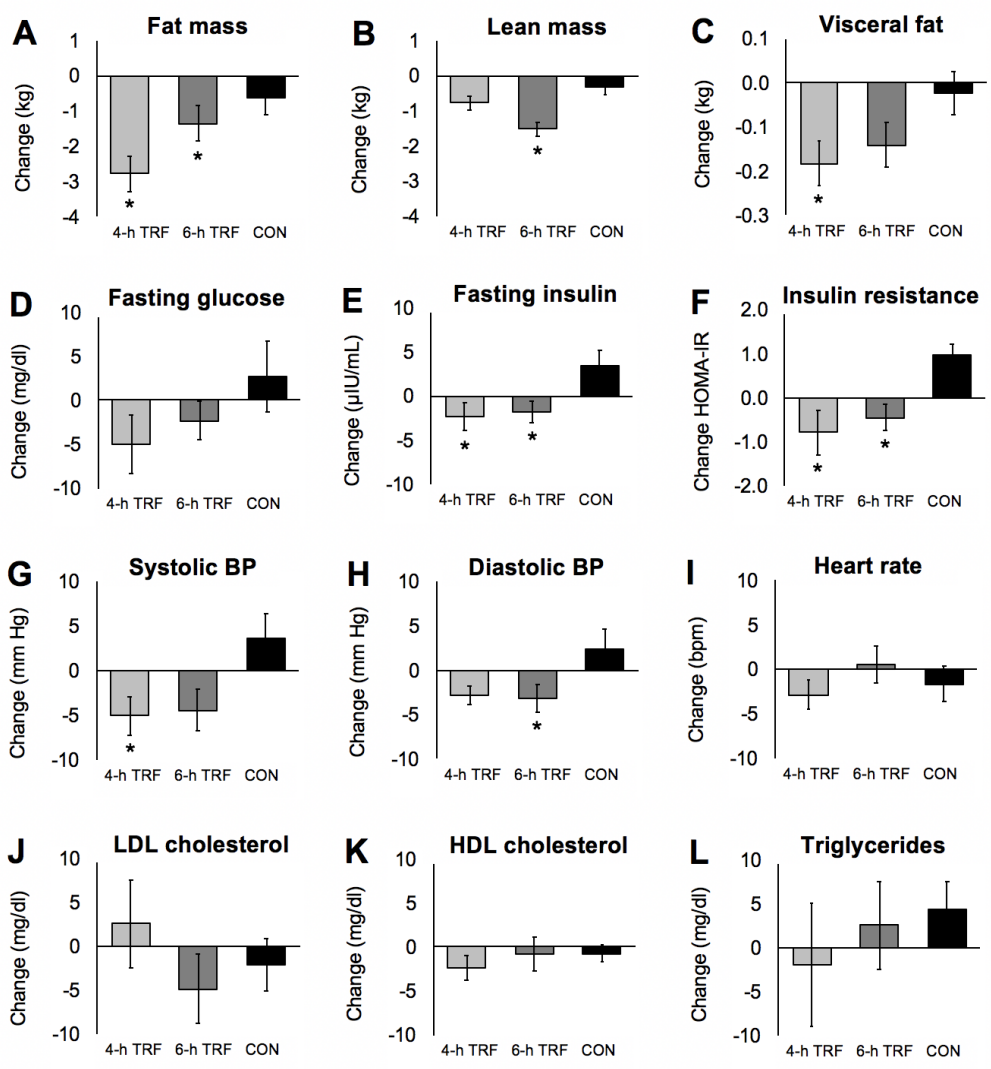


Figure 4. Body composition and metabolic risk markers

After 8-weeks, fat mass **(A)** decreased in both the 4-h and 6-h TRF groups, relative to controls. Lean mass **(B)** decreased only by 6-h TRF, while visceral fat mass **(C)**, was reduced only by 4-h TRF, versus controls. Fasting glucose **(D)** was not affected by either 4-h or 6-h TRF. Fasting insulin **(E)** and insulin resistance **(F)** decreased in both 4-h TRF and 6-h TRF groups, when compared to controls, with no difference between groups. Systolic blood pressure **(G)** decreased in the 4-h TRF group only, while diastolic blood pressure **(H)** was reduced in the 6-h TRF group only, versus controls. Heart rate **(I)** remained unchanged. Plasma lipids, including LDL cholesterol **(J)**, HDL cholesterol **(K)** and triglycerides **(L)**, did not change. Values reported as mean ± SEM. *Change score (baseline to week 8) significantly different from controls ($P < 0.05$, ANOVA).

4-h and 6-h TRF produce comparable reductions in oxidative stress but do not affect inflammatory markers

8-isoprostane is a marker of oxidative stress to lipids. Change in plasma levels of 8-isoprostane by week 8 in the 4-h TRF group (Δ = -13 $\pm$ 6 pg/ml, 37% reduction) and 6-h TRF group (Δ = -12 $\pm$ 4 pg/ml, 34% reduction), was significantly different (P = 0.03) from controls (Δ = 3 $\pm$ 3 pg/ml), with no significant differences between intervention groups (**Figure 5A**). In contrast, neither intervention had any impact on inflammatory markers. For instance, change in plasma levels of TNF-alpha by week 8 were not significantly different (P = 0.54) between the 4-h TRF (Δ = -2.4 $\pm$ 2.6 pg/ml), 6-h TRF (Δ = 0.4 $\pm$ 2.4 pg/ml), or control groups (Δ = 0.2 $\pm$ 1.8 pg/ml) (**Figure 5B**). Similarly, change in plasma levels of IL-6 by week 8 were not significantly different (P = 0.53) between the 4-h TRF (Δ = 2.4 $\pm$ 1.0 pg/ml), 6-h TRF (Δ = 0.4 $\pm$ 1.7 pg/ml), or control groups (Δ = 0.5 $\pm$ 1.1 pg/ml) (**Figure 5C**).

The reductions in oxidative stress are consistent with other human trials of intermittent fasting. In a 5-week trial of 6-h TRF, circulating 8-isoprostane was reduced by 14% in men with obesity and prediabetes, even without weight loss [32]. Correspondingly, 8-weeks of alternate day fasting decreased several markers of oxidative stress, including 8-isoprostane, 4-hydroxynonenal adducts, protein carbonyls, and nitrotyrosine [18]. As for inflammatory markers, human trials of intermittent fasting report no change in IL-6, TNF-alpha, or CRP [3, 9, 32, 34, 51]. Taken together, TRF along with other forms of fasting, have little effect on inflammation but have potent effects on oxidative stress.

It is also likely that the decrease in oxidative stress noted here, is related to improvements in insulin resistance. Studies have demonstrated a clear link between insulin resistance and oxidative stress. Under oxidative conditions, insulin signaling is impaired, resulting in insulin resistance of the cell [81,

82]. Other studies have shown improvement in insulin sensitivity when administering antioxidants, such as vitamin E [83]. Therefore, we could speculate that one of the mechanisms by which intermittent fasting improves insulin resistance is by decreasing oxidative stress.

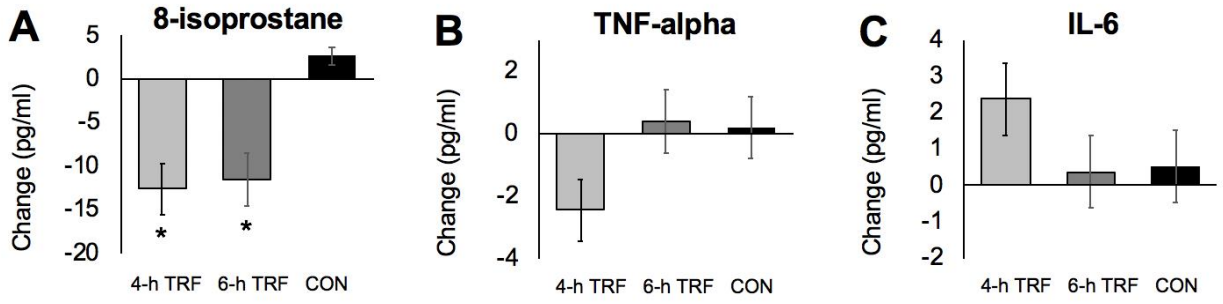


Figure 5. Oxidative stress and inflammatory markers

After 8-weeks, both the 4-h and 6-h TRF interventions decreased 8-isoprostane levels (marker of oxidative stress to lipids), with no difference between groups **(A)**. The 4-h and 6-h TRF diet did not have any effect on the inflammatory markers, TNF-alpha **(B)** or IL-6 **(C)**. Values reported as mean ± SEM. *Change score (baseline to week 8) significantly different from controls ($P < 0.05$, ANOVA).

Adverse events

No serious adverse events were reported. Mild adverse events such as dizziness, nausea, headaches, and diarrhea peaked at week 2 in both TRF interventions, relative to controls, but disappeared by week 3 and did not reoccur during the trial (**Figure 6A-D**). Levels of fatigue did not change over the course of the trial relative to controls (**Figure 6E**). Constipation (**Figure 6F**) and dry mouth (**Figure 6G**) were observed in both the 4-h and 6-h TRF groups at week 2 relative to controls, and these issues persisted throughout some or most of the study. Occurrences of irritability remained low throughout the trial and were not significantly different from controls (**Figure 6H**). These findings suggest that mild adverse

effects, such as dizziness, nausea, headaches, diarrhea and constipation may occur at the onset of TRF, but disappear quickly when the participant becomes adjusted to the diet.

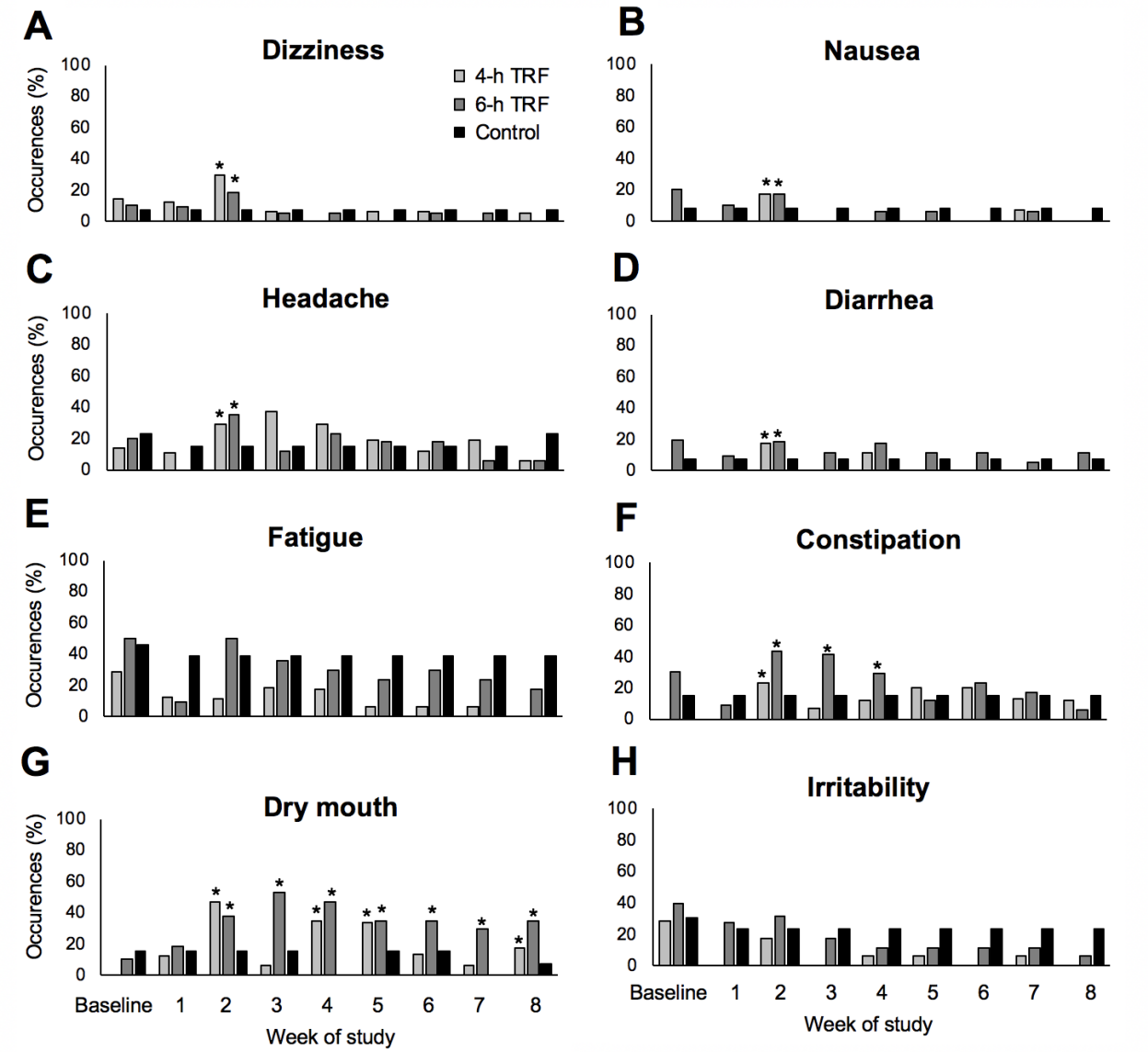


Figure 6. Adverse events

Adverse events such as dizziness **(A)**, nausea **(B)**, headaches **(C)**, and diarrhea **(D)** peaked at week 2 in both the 4-h and 6-h TRF interventions, but disappeared by week 3 and did not reoccur during the trial. Levels of fatigue **(E)** did not change. Constipation **(F)** and dry mouth **(G)** were observed in both the 4-h and 6-h TRF groups at week 2, and these issues persisted during most of the trial. Irritability

(H) remained low throughout the trial. Values reported as percent occurrences at each week of the study. *Percent occurrences significantly different from controls ($P < 0.05$, ANOVA) at each time point.

4-h and 6-h TRF produce similar reductions in energy intake without calorie counting

As shown in **Table 2**, change in energy intake by week 8 in the 4-h TRF group (Δ = -528 $\pm$ 102 kcal/d, -2209 $\pm$ 427 kJ/d, 30% reduction) and 6-h TRF group (Δ = -566 $\pm$ 142 kcal/d, -2368 $\pm$ 594 kJ/d, 29% reduction), was significantly different ($P = 0.02$) versus controls (Δ = -105 $\pm$ 52 kcal/d, 439 $\pm$ 217 kJ/d), with no significant differences between intervention groups. TRF is a unique weight loss regimen in that it does not require calorie counting. Participants are simply asked to consume all their food for the day within a specified time frame, and water fast for the remaining hours of the day. We show here that by simply limiting the eating window to 4-h or 6-h, participants with obesity naturally decrease energy intake by ~550 kcal/d (2300 kJ/d). From a clinical standpoint, these findings are paramount. One of the main reasons for participant attrition during daily CR and alternate day fasting trials is frustration with having to vigilantly monitor energy intake on a regular basis [4, 84, 85]. TRF regimens are able to side-step this requirement by allowing participants to simply watch the clock instead of monitoring calories, while still producing weight loss. Human trials of TRF with longer durations (>12 month) will be needed to see if these changes in energy intake persist long-term.

TRF appears to produce comparable reductions in energy intake (20-30%) as daily CR. Interestingly, despite similar degrees of energy restriction, TRF produces less weight loss compared to daily CR over the same duration of time. For instance, recent controlled trials of CR report 4-7% weight loss over 2-3 months in adults with obesity [4, 86-88], while TRF trials report 3-4% weight loss [7, 8, 62]. The reason for this discrepancy is unclear. It is possible however, that estimates of energy restriction in the TRF

trials are inaccurate since this data was quantified via food records. It is well known that participants with obesity underreport energy intake by 20-40% in food diaries [89, 90]. Many of the CR trials, on the other hand, used doubly labeled water to assess energy restriction (gold standard method) [4, 86, 87]. In order to ascertain whether TRF truly produces 20-30% energy restriction, future trials should implement the doubly labeled water technique. Studies that directly compare the effects of TRF to CR are also undoubtedly needed, as none have been performed to date.

We also assessed changes in diet quality during TRF. It is conceivable that limiting the eating window to 4 or 6 hours per day could lead to the increased consumption of energy dense foods and compensatory drinking (i.e. increased diet soda and caffeine intake). As such, we examined whether key diet quality indicators, such as sugar, saturated fat, cholesterol, fiber and sodium intake, changed from baseline to week 8. Results reveal that changes in these parameters of diet quality by week 8 were not significantly different between the 4-h TRF, 6-h TRF, or control groups (**Table 2**). Intakes of sugar, saturated fat, cholesterol, fiber and sodium were similar to what is typically consumed by the average American at baseline and post-treatment [91, 92]. In addition, changes in diet soda, sugar sweetened soda, caffeinated beverages excluding sodas (caffeinated coffee, caffeinated tea, energy drinks), or alcohol intake by week 8 were not significantly different between the 4-h TRF, 6-h TRF, or control groups (**Table 2**). Although the present short-term (8-week) trial shows no change in these key indicators of diet quality, these findings will need confirmation by a well-powered study that specifically examines the impact of 4-h and 6-h TRF on these parameters.

Table 5. Dietary intake and physical activity

Variable	4-hour TRF			6-hour TRF			Control		
Dietary intake	**Baseline**	**Week 8**	**Change**	**Baseline**	**Week 8**	**Change**	**Baseline**	**Week 8**	**Change**
Energy (kcal)	1752 ± 196	1224 ± 185	-528 ± 102*	1931 ± 222	1365 ± 126	-566 ± 142*	1638 ± 121	1533 ± 125	-105 ± 52
Protein (%)	19 ± 1	18 ± 1	-1 ± 1	17 ± 1	20 ± 1	3 ± 1	19 ± 1	18 ± 1	-1 ± 1
Carbohydrates (%)	42 ± 3	46 ± 2	4 ± 3	42 ± 1	40 ± 2	-2 ± 3	38 ± 3	40 ± 3	2 ± 1
Total sugar (%)	12 ± 1	15 ± 2	3 ± 2	13 ± 1	11 ± 1	-2 ± 1	13 ± 2	14 ± 2	1 ± 1
Fat (%)	39 ± 3	36 ± 2	-3 ± 3	41 ± 2	40 ± 3	-1 ± 3	43 ± 2	42 ± 3	-1 ± 1
Saturated fat (%)	15 ± 1	13 ± 1	-2 ± 1	17 ± 1	16 ± 1	-1 ± 1	17 ± 3	17 ± 3	0 ± 1
Monounsaturated fat (%)	14 ± 1	13 ± 1	-1 ± 1	14 ± 1	14 ± 1	0 ± 1	16 ± 4	16 ± 4	0 ± 1
Polyunsaturated fat (%)	10 ± 1	10 ± 2	0 ± 1	10 ± 3	10 ± 1	0 ± 3	10 ± 1	9 ± 1	-1 ± 1
Cholesterol (mg)	305 ± 39	177 ± 26	-128 ± 48	335 ± 43	251 ± 29	-84 ± 48	326 ± 43	271 ± 40	-55 ± 25
Fiber (g)	15 ± 3	13 ± 3	-2 ± 2	16 ± 3	17 ± 4	1 ± 4	18 ± 5	16 ± 4	-2 ± 1
Sodium (mg/d)	2470 ± 328	1747 ± 274	-723 ± 279	2664 ±430	2432 ± 311	-232 ± 348	2314 ± 164	2193 ± 179	-121 ± 161
Beverage intake									
Diet soda (ml/d)	21 ± 15	16 ± 9	-5 ± 13	37 ± 16	22 ± 9	-15 ± 21	34 ± 21	17 ± 17	-17 ± 13
Sugar sweetened soda (ml/d)	123 ± 92	96 ± 68	-27 ± 33	53 ± 38	27 ± 13	-26 ± 37	20 ± 12	71 ± 38	51 ± 45
Caffeinated beverages (ml/d)	131 ± 38	172 ± 54	41 ± 39	226 ± 52	202 ± 64	-24 ± 55	379 ± 93	260 ± 113	-119 ± 92
Alcohol (g/d)	6 ± 3	4 ± 2	-2 ± 1	5 ± 2	4 ± 2	-1 ± 1	2 ± 1	2 ± 1	0 ± 1
Physical activity									
Steps/d	7787 ± 859	7190 ± 669	-597 ± 702	7312 ± 659	7365 ± 778	53 ± 457	9477 ± 736	9836 ± 883	359 ± 533

Values reported as mean ± SEM.

Change: Absolute change score from baseline to week 8.

* $P < 0.05$, change score significantly different from controls by ANCOVA.

Limitations

This study has several limitations. First, our sample size was small and we may have been underpowered to detect differences between groups for certain secondary outcome measures. In retrospect, it would have been helpful to perform calculations for key secondary outcomes (e.g. LDL cholesterol, triglycerides, and fasting glucose) in addition to our primary outcome, to ensure sufficient power. Second, we did not evaluate the effects of the 4-h or 6-h regimens at different times in the day (early TRF versus late TRF). Insulin sensitivity has been purported to be higher in the morning than in the evening [65, 93]. Thus, it's possible that if these regimens were shifted earlier in the day, more pronounced reductions in insulin resistance would have been noted. Third, we only measured one indicator of oxidative stress, 8-isoprostane. It would have been useful to determine if other measures of oxidative stress (i.e. 4-hydroxynonenal adducts, protein carbonyls, and nitrotyrosine) are also improved with this diet. Fourth, these TRF interventions failed to produce clinically significant weight loss, i.e. 5% from baseline [94], over 8-weeks. Longer-term trials will be required to see if these diets can indeed be implemented to produce the 5% weight loss necessary to observe lasting benefits to overall health.

Conclusion

Our study is the first randomized controlled trial to compare the weight loss efficacy of 4-h versus 6-h TRF in adults with obesity. Findings from this trial suggest that 4-h TRF does not produce superior weight loss versus 6-h TRF. Both fasting regimens induce mild reductions in body weight over 8 weeks (~3%), and show promise as interventions for weight loss. Reductions in insulin resistance, blood pressure and oxidative stress were also noted, which bode well for the use of these regimens in preventing cardiometabolic disease. Compliance was similar for 4-h and 6-h TRF, and both regimens reduced daily energy intake by ~550 kcal/d, 2300 kJ/d (30% reduction), without calorie counting. Though these findings are promising, future trials will be needed to examine the feasibility of TRF long-term, and also examine whether the weight loss and cardiometabolic benefits can be sustained over longer periods of time.

STAR METHODS

Key resources table

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Critical Commercial Assays		
Human TNF-alpha Quantikine ELISA kit	R&D Systems	DTA00D
Human IL-6 Quantikine ELISA kit	R&D Systems	D6050
8-Isoprostane ELISA kit	Cayman Chemical	516351
Software		
SPSS v.25.0	IBM	www.ibm.com

Contact for reagent and resource sharing

Further information and requests for resources and reagents should be directed to the Principal Investigator, Dr. Krista Varady (varady@uic.edu). For specific cases of biospecimen and data sharing requests, such requests will require a Material Transfer Agreement and/or a Data Use Agreement and will be managed by the University of Illinois at Chicago Material Transfer Office, which abides by the Uniform Biological Material Transfer Agreement (UBMTA).

METHOD DETAILS

Participant selection

The experimental protocol was approved by the University of Illinois Chicago Office for the Protection of Research Subjects, and all research participants gave their written informed consent to participate in the trial. Prior to enrolling participants, the trial was preregistered on clinicaltrials.gov (NCT03867773). The trial was conducted between February 2019 to October 2019. Participants were recruited from the Chicago area via advertisements placed around the University of Illinois Chicago campus. Participants were screened via a questionnaire, BMI assessment, and pregnancy test. A total of 82 participants

were consented and were assessed for eligibility (**Figure 2**). Of these 82 participants, 24 were excluded because they did not meet one or more inclusion criteria. Inclusion criteria was as follows: male; female; body mass index (BMI) between 30.0 and 49.9 kg/m^2; age between 18 and 65 years; sedentary (light exercise less than 1 h per week) or moderately active (moderate exercise 1 to 2 h per week); weight stable for 3 months prior to the beginning of the study (gain or loss <4 kg); and able to give written informed consent. Exclusion criteria: diabetes mellitus; use of medications that could affect study outcomes; night shift workers; perimenopausal or otherwise irregular menstrual cycle; pregnant or trying to become pregnant; and current smokers.

Study design

A 10-week randomized parallel-arm trial was implemented to compare the effects of 4-h and 6-h TRF versus controls on body weight and secondary outcome measures. The trial consisted of a 2-week baseline period followed by an 8-week TRF intervention period.

Baseline period (Week B1 and B2): Before commencing the study, all subjects participated in a 2-week baseline weight stabilization period. During this period, participants were requested to remain weight stable by consuming their usual diet and not changing their physical activity habits. **TRF protocols (Week 1-8):** During the 8-week intervention period, the 4-h TRF group was instructed to eat ad libitum from 3:00-7:00 pm daily, and fast from 7:00-3:00 pm (20-h fast). The 6-h TRF group was instructed to eat ad libitum from 1:00-7:00 pm daily, and fast from 7:00-1:00 pm (18-h fast). During the 4-h and 6-h feeding windows, there were no restrictions on types or quantities of foods consumed. Moreover, participants were not required to monitor caloric intake during this ad libitum feeding period. During

the fasting period, participants were encouraged to drink plenty of water and were permitted to consume energy-free beverages, such as black tea, coffee, and diet sodas.

Control group protocol: Controls were instructed to maintain their weight throughout the trial, and not to change their eating or physical activity habits. Controls received no diet advice but visited the research center at the same frequency as the intervention groups to alleviate any investigator-interaction bias. Controls who completed the 10-week trial received 4 sessions of free weight loss counseling at the end of the study.

OUTCOME MEASURES

Body weight and body composition

The primary outcome of the study was change in body weight. Body weight was assessed to the nearest 0.25 kg every week at the research center without shoes and in light clothing using a digital scale (HealthOMeter, Boca Raton, FL). Height was assessed during the screening visit using a wall-mounted stadiometer (HealthOMeter, Boca Raton, FL) to the nearest 0.1 cm. Body composition (fat mass, lean mass, visceral fat mass) was measured at baseline and week 8 using dual x-ray absorptiometry (DXA; iDXA, General Electric Inc).

Adherence to the TRF protocols

Adherence to the 4-h and 6-h TRF windows was measured using a daily adherence log, which recorded the times each participant started and stopped eating each day. If the log indicated that the participant ate within the prescribed 4-h or 6-h window, that day was labeled “adherent”. If the log indicated that the participant consumed food outside of the prescribed 6-h or 4-h feeding windows, that day was

labeled as “non-adherent”. Adherence to the TRF diet was assessed as the number of adherent days per week. Throughout the trial, participants met with the study coordinator on a weekly basis (after the weigh in) to review the adherence log. At each of these meetings, the study coordinator emphasized the importance of eating within the prescribed window. Participants were also encouraged to discuss any issues they had with adhering to the diet during these meetings.

Metabolic disease risk factors

Blood samples were collected after a 12-h fast at week 1 (before starting the intervention) and at week 8, between 6:00-9:00 am. All blood draws were performed at the Human Nutrition Research Unit at the University of Illinois at Chicago. Blood was centrifuged for 20 min at 520 x g and 4°C to separate plasma from red cells and stored at -80°C until analyzed. Fasting plasma total cholesterol, direct LDL cholesterol, HDL-cholesterol, triglycerides, glucose and insulin concentrations were measured by a commercial lab (Medstar, Chicago, IL). Insulin resistance (IR) was calculated using the HOMA (Homeostasis Model Assessment) method, by applying the following formula: [HOMA-IR = Fasting insulin (µlU/ml) × Fasting glucose (mg/dL) / 405]. Blood pressure and heart rate were measured in triplicate using a digital automatic blood pressure/heart rate monitor (Omron HEM 705 LP, Kyoto, Japan) with the participant in a seated position after a 10-min rest.

Inflammatory markers and oxidative stress

Plasma levels of the inflammatory cytokines, TNF-alpha and IL-6, and the oxidative stress marker, 8-isoprostane, were measured by ELISA (R&D Systems, Minneapolis, MN; Cayman Chemical Company; Ann Arbor, MI, respectively) on a Bio Rad Microplate reader (Bio-Rad Laboratories; Hercules, CA).

Adverse events

Neurological issues (dizziness, headache, fatigue, and irritability) and gastrointestinal issues (nausea, diarrhea, constipation, and dry mouth) were assessed by an adverse events questionnaire at baseline and during each week of the intervention period.

Dietary intake and physical activity

TRF and control participants completed a 7-d food record during the baseline period and at week 8. A dietitian provided 15 min of instruction to each participant on how to complete the food records. These instructions included information and reference guides on how to estimate portion sizes and record food items in sufficient detail to obtain accurate estimates of dietary intake. Participants were not required to weigh foods but were asked to measure the volume of foods consumed with household measures (i.e. measuring cups and measuring spoons). The timing of food intake (for each beverage or food item) was also recorded in the food record. The records were collected at the weigh-in at baseline and week 8 and were reviewed by the dietitian for accuracy and completeness. The food analysis program, Nutritionist Pro (Axxya Systems, Stafford, TX) was used to calculate the total daily intake of energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, protein, carbohydrate, total sugar, cholesterol, fiber, sodium, and alcohol. Consumption of diet sodas, sugar-sweetened sodas, and caffeinated beverages excluding sodas (caffeinated coffee, caffeinated tea, energy drinks) are presented as mean intakes by volume (ml/d).

All participants were asked to maintain their level of physical activity throughout the entire trial. Step counts were measured over 7-d during the baseline period and at week 8 by a Fitbit Alta HR (Fitbit, San

Francisco, CA). Participants were instructed to wear the device all day and night (except while showering).

QUANTIFICATION AND STATISTICAL ANALYSES

Power and sample size

For the sample size calculation, we estimated that the 4-h TRF group would lose 5% and the 6-h TRF group would lose 2% of body weight over 8 weeks [7]. We calculated that n = 16 participants per group would provide 80% power to detect a significant difference of 3% in body weight between the 4-h and 6-h TRF groups by week 8, using an independent samples t-test with $\alpha = 0.05$. We anticipated a dropout rate of 20%. Thus, we initially aimed to recruit 57 participants (n = 19 per group), assuming that 48 participants (n = 16 per group) would complete the trial.

Randomization

Participants were randomized in a 1:1:1 ratio to a 4-h TRF group, a 6-h TRF group, or a no-intervention control group. Randomization was performed by a stratified random sampling procedure by sex, age (18-42 y/ 43-65 y), and BMI (30.0-39.9 kg/m^2 / 40.0-49.9 kg/m^2).

Statistical analyses

Statistical analyses were performed using SPSS v.25.0 for Mac (SPSS Inc.). A two-tailed P value of less than 0.05 was considered statistically significant. All data are presented as mean $\pm$ standard error of the mean (SEM). Tests for normality were included in the model, and all data were found to be normally distributed. Differences between treatment arms (4-h TRF, 6-h TRF, and control) were

evaluated as change scores (from baseline to week 8) using ANOVA. Change scores are represented by "Δ" in the results text. Pearson correlations were performed to assess the relationship between weight loss and change from baseline in the duration of the fasting window. Data were included for 58 participants, and means were estimated using an intention-to-treat analysis using last observation carried forward. All dropouts occurred during week 1 or 2 of the study. Baseline body weight, height and BMI were collected for all dropouts (4-h TRF: n = 3, 6-h TRF: n = 1, Control: n = 5). None of the dropouts attended the baseline DXA scan visit, thus, no body composition data are available for these participants. Moreover, none the dropouts returned food records or adherence logs, so there is no dietary intake or compliance data for the subjects. Only a few dropouts attended the baseline blood draw/blood pressure visit (4-h TRF: n = 1, 6-h TRF: n = 1, Control: n = 3), so data for these parameters are limited. TNF-alpha, IL-6, and 8-isoprostane data are not available for dropouts as not enough blood could be collected from these participants.

Acknowledgments

This study was supported by R01DK119783 from the National Institutes of Health. The authors would like to thank the study participants for their time and effort in participating in the trial. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author contributions

SC designed the research, conducted the clinical trial, analyzed the data, performed the statistical analysis, and wrote the manuscript; KG, FK, ME, EW and VP assisted with the conduction of the clinical

trial; SL and MLO analyzed the food records; KAV designed the research, analyzed the data, and wrote the manuscript. All authors helped interpret the data, revised the manuscript for critical content, and approved the final version of the manuscript.

IV. MANUSCRIPT 2

BRIEF REPORT

The effect of 4-h versus 6-h time restricted feeding on sleep quality, insomnia severity and obstructive sleep apnea in adults with obesity

Nutrition and Health, 2021;02601060211002347

Sofia Cienfuegos, Kelsey Gabel, Faiza Kalam, Mark Ezpeleta, Vicky Pavlou, Shuhao Lin, Eric Wiseman, Krista A. Varady

Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, IL

Correspondence and reprint requests:

Krista Varady, PhD

Professor of Nutrition

Department of Kinesiology and Nutrition, University of Illinois at Chicago

1919 West Taylor Street, Room 532, Chicago, IL, 60612, Tel: 312-996-7897, Email: varady@uic.edu

Running head: Time restricted feeding and sleep

Funding: National Institutes of Health, NIDDK, R01DK119783

Conflict of interest: The authors declare no conflict of interest.

Trial registration: Clinicaltrials.gov NCT03867773

1. Abstract

Background: Time restricted feeding (TRF) involves deliberately restricting the times during which energy is ingested. Preliminary findings suggest that 8-10-h TRF improves sleep. However, the effects of shorter TRF windows (4-6-h) on sleep, remain unknown.

Objective: This study compared the effects of 4-h versus 6-h TRF on sleep quality and duration.

Methods: Adults with obesity (n = 49) were randomized into 1 of 3 groups: 4-h TRF (eating only between 3-7 pm), 6-h TRF (eating only between 1-7 pm), or a control group (no meal timing restrictions) for 8 weeks. **Results:** After 8 weeks, body weight decreased ($P < 0.001$) similarly by 4-h TRF (-3.9 ± 0.4 kg) and 6-h TRF (-3.4 ± 0.4 kg), versus controls. Insomnia severity decreased ($P < 0.05$) in the 6-h TRF group only (baseline: 8.3 ± 1.2, week 8: 5.5 ± 1.1), versus controls. Sleep quality, measured by the Pittsburgh Sleep Quality Index (PSQI), did not change by 4-h TRF (baseline: 5.9 ± 0.7; week 8: 4.8 ± 0.6) or 6-h TRF (baseline: 6.4 ± 0.8; week 8: 5.3 ± 0.9), versus controls. Wake time, bedtime, and sleep duration remained unchanged. Percent of subjects reporting obstructive sleep apnea symptoms did not change by 4-h TRF (baseline: 44%; week 8: 25%) or 6-h TRF (baseline: 47%; week 8: 20%), versus controls. **Conclusion:** These findings suggest that 4-h and 6-h TRF have little impact on sleep quality, duration, or risk of obstructive sleep apnea. However, insomnia severity may be improved slightly by 6-h TRF.

Key words: Intermittent fasting, time restricted feeding, sleep quality, insomnia, obstructive sleep apnea, obesity, weight loss

Introduction

Time restricted feeding (TRF) is a type intermittent fasting that has gained substantial popularity over recent years. The diet involves confining the period of eating to 4-10 h and water fasting (with zero calorie beverages permitted) for the rest of the day. Although these diets have shown favorable effects for body weight and metabolic health, only a handful of studies have examined the effect of TRF on sleep [7, 8, 13, 62]. In a recent study by Wilkinson et al [8], 10-h TRF improved morning restfulness but had no effect on sleep quality after 12 weeks in subjects with metabolic syndrome. In another study of 10-h TRF by Gill and Panda [62], overweight participants experienced improved sleep quality after 16 weeks of intervention. In contrast, two other studies of TRF show no effect on sleep parameters. Gabel et al [7] demonstrated no change in sleep quality or sleep duration after 12 weeks of 8-h TRF in subjects with obesity. Similarly, Hutchison et al [13] showed no effect of 9-h TRF on sleep duration in men with obesity. In view of these equivocal findings, the effects of TRF on sleep still remain uncertain.

We recently performed a study to examine the effect shorter eating windows during TRF (4-h versus 6-h) on body weight [95]. Results reveal that both 4-h TRF and 6-h TRF produced nearly identical weight loss (~3%) after 8 weeks of intervention. Since reductions in body weight are related to improved sleep quality and duration [42, 96, 97], we were interested in seeing whether sleep would be ameliorated with these TRF interventions. Accordingly, the aim of this secondary analysis was to compare the effect of 4-h versus 6-h TRF on sleep quality, insomnia severity and risk obstructive sleep apnea, versus a control group that had no meal timing restrictions.

Methods

Subject selection

This is a secondary analysis of a 10-week randomized parallel-arm trial comparing the effects of 4-h and 6-h TRF versus controls on body weight in adults with obesity [95]. Inclusion criteria were as follows: female; male; body mass index (BMI) between 30.0 and 49.9 kg/m2; age between 18 and 65 years; sedentary (light exercise less than 1 h per week) or moderately active (moderate exercise 1 to 2 h per week); weight stable for >3 months prior to the beginning of the study (gain or loss <4 kg); and able to give written informed consent. Subjects who were smokers; diabetic; taking weight loss medications; night-shift workers; perimenopausal or pregnant, were excluded. The University of Illinois Chicago Office for the Protection of Research Subjects approved the experimental protocol, and all research participants gave their written informed consent to participate in the trial.

Time restricted feeding protocol

Participants were randomized by a stratified random sample (based on age, sex, and BMI) into 1 of 3 groups: 4-h TRF, 6-h TRF, or a no-intervention control group. Briefly, the trial consisted of a 2-week baseline weight stabilization period followed by an 8-week TRF intervention period. During the 8-week intervention, the 4-h TRF group was instructed to eat ad libitum from 3 to 7 pm daily, and fast from 7 to 3 pm (20-h fast). The 6-h TRF group was instructed to eat ad libitum from 1 to 7 pm daily, and fast from 7 to 1 pm (18-h fast). During the feeding windows, TRF participants were not required to monitor caloric intake and there were no restrictions on types or quantities of foods consumed. During the fasting window, TRF participants were encouraged to drink plenty of water and were permitted to

consume energy-free beverages, such as black tea, coffee, and diet sodas. Controls were instructed to maintain their weight throughout the trial, and not to change their eating or physical activity habits.

Body weight, diet compliance, and physical activity

Body weight was assessed to the nearest 0.25 kg every week without shoes and in light clothing using a digital scale (HealthOMeter, Boca Raton, FL). Body composition (fat mass, lean mass, visceral fat mass) was measured at baseline and at week 8 using dual x-ray absorptiometry (DXA; iDXA, General Electric Inc). Adherence to the 6-h and 4-h TRF windows was measured using a daily adherence log, which recorded the times each subject started and stopped eating each day. If the log indicated that the subject ate within the appropriate 6-h or 4-h window, that day was labeled "adherent". If the log indicated that the subject consumed food outside of the 6-h or 4-h feeding windows, that day was labeled as "non-adherent". Adherence to the TRF diet was assessed as the number of adherent days per week. All subjects were asked to maintain their level of physical activity throughout the entire trial. Activity level (steps/d) was measured over a 7-d period during baseline and at week 8 by Fitbit Alta HR (Fitbit, San Francisco, CA).

Sleep measures

All questionnaires were administered during the baseline period (pre-intervention) and at week 8 (last week of intervention). The severity of insomnia in the past week was measured by the Insomnia Severity Index (ISI), which is a 7-item questionnaire [98]. Each item is rated by a 5-point Likert scale (where 0 indicates no problem, and 4 indicates a very severe problem) yielding a total score of 0-28. The total score for the ISI is interpreted as follows: no clinically significant insomnia (0-7), sub-

threshold insomnia (8-14), moderate severity insomnia (15-21), and severe insomnia (22-28). Sleep quality, timing and duration were measured by the Pittsburgh Sleep Quality Index (PSQI) [99]. This 19-item self-report measures total sleep quality in the past month, yielding a total score of 0-21. A PSQI total score greater than 5 indicates poor sleep quality. The questionnaire also assesses usual bedtime, usual wake time, and hours of actual obtained sleep. Risk of obstructive sleep apnea was estimated using the Berlin Questionnaire [100].

Statistical analyses

All data are presented as means ± SEM. Statistical analyses were performed using SPSS v.25.0 for Mac (SPSS Inc.). A two-tailed P value of less than 0.05 was considered statistically significant. Data were analyzed for completers only. Tests for normality were included in the model, and all data were found to be normally distributed. At baseline, differences between treatment arms (4-h TRF, 6-h TRF, and control) were tested by a one-way ANOVA with a Tukey post-hoc test (continuous variables) or McNemar test (categorical variables). At week 8, differences across treatment arms (4-h TRF, 6-h TRF, and control) were evaluated as change scores (from baseline to week 8) using ANCOVA with baseline as a covariate. If the overall ANCOVA across the three arms was significant, pairwise comparisons were performed to evaluate differences between arms using Bonferroni post-hoc tests.

Results

Subject baseline characteristics and dropouts

As previously reported [101], n = 82 participants were assessed for eligibility and n = 24 were excluded because they did not meet one or more inclusion criteria. A total of 58 participants were randomized into the 4-h TRF group (n = 19), 6-h TRF group (n = 20), or the control group (n = 19). At the end of the trial, the number of completers was as follows: 4-h TRF group (n = 16), 6-h TRF group (n = 19), or the control group (n = 14). There were no significant differences between groups for any parameter at baseline (**Table 1**). Participants who completed the study were primarily middle-age, women with obesity who were normotensive and normocholesterolemic but insulin resistant [101].

Table 6. Body weight, body composition, and sleep variables after 8 weeks of time restricted feeding

	4-h TRF (n = 16)			6-h TRF (n = 19)			Controls (n = 14)		
	Baseline	**Week 8**	**Change**	**Baseline**	**Week 8**	**Change**	**Baseline**	**Week 8**	**Change**
Demographics									
Age	49 ± 2	--	--	46 ± 3	--	--	45 ± 2	--	--
Sex (Female/Male)	14 / 2	--	--	18 / 1	--	--	12 / 2	--	--
Anthropometrics									
Body weight (kg)	101.0 ± 4.8	97.1 ± 3.6	-3.9 ± 0.4 *	99.3 ± 4.6	95.9 ± 4.4	-3.4 ± 0.4 *	92.7 ± 4.5	92.9 ± 4.4	0.2 ± 0.5
Fat mass (kg)	48.4 ± 2.8	45.6 ± 3.4	-2.8 ± 0.4 *	47.5 ± 3.4	46.1 ± 3.4	-1.4 ± 0.3 *	42.5 ± 3.3	41.9 ± 3.2	-0.6 ± 0.4
Lean mass (kg)	52.4 ± 2.3	51.6 ± 2.2	-0.8 ± 0.4 *	50.2 ± 2.6	48.7 ± 2.6	-1.5 ± 0.2 †*	47.6 ± 2.8	47.3 ± 2.8	-0.3 ± 0.2
Visceral fat mass (kg)	1.4 ± 0.2	1.2 ± 0.1	-0.2 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	-0.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	0 ± 0.1
Compliance with diet (d/week)	--	6.2 ± 0.2	--	--	6.2 ± 0.1	--	--	--	--
Steps/d	7787 ± 859	7190 ± 669	-597 ± 702	7312 ± 659	7365 ± 778	53 ± 457	9477 ± 736	9836 ± 883	359 ± 533
Insomnia severity index (ISI)									
Total score	4.4 ± 1.0	4.7 ± 0.9	0.3 ± 0.9	8.3 ± 1.2	5.5 ± 1.1	-2.8 ± 1.0 *	6.5 ± 1.2	6.9 ± 1.5	0.4 ± 1.2
Pittsburgh Sleep Quality Index (PSQI)									
Total score	5.9 ± 0.7	4.8 ± 0.6	-1.1 ± 0.8	6.4 ± 0.8	5.3 ± 0.9	-1.1 ± 0.5	6.7 ± 0.7	6.5 ± 0.7	-0.2 ± 1.1
Wake time (h:min)	5:40 ± 0:20	5:40 ± 0:20	0:00 ± 0:20	6:30 ± 0:25	6:25 ± 0:20	-0:05 ± 0:25	5:35 ± 0:30	5:45 ± 0:25	0:10 ± 0:25
Bedtime (h:min)	22:40 ± 0:20	22:30 ± 0:20	-0:10 ± 0:20	22:40 ± 0:25	22:35 ± 0:30	-0:05 ± 0:30	22:50 ± 0:30	22:45 ± 0:30	-0:05 ± 0:30
Sleep duration (h)	7.0 ± 0.3	7.2 ± 0.2	0.2 ± 0.2	7.8 ± 0.3	7.8 ± 0.3	0 ± 0.2	6.8 ± 0.4	7.0 ± 0.3	0.2 ± 0.3
Berlin questionnaire									
High risk of obstructive sleep apnea (%)	44%	25%	-19%	47%	20%	-27%	46%	54%	8%

Continuous variables reported as mean ± SEM. Risk of obstructive sleep apnea reported as % occurrences. Change: Absolute change score from baseline to week
No significant differences between groups for any parameter at baseline (ANOVA for continuous variables; McNemar test for categorical variables).
*Change score significantly different from control group (P < 0.05, ANCOVA with baseline as a covariate).
† Change score significantly different from 4-h TRF group (P < 0.05, ANCOVA with baseline as a covariate).

Body weight, diet compliance, and physical activity

Weight loss by week 8 in the 4-h TRF group (Δ = -3.9 ± 0.4 kg) and 6-h TRF group (Δ = -3.4 ± 0.4 kg), was significantly different (P < 0.001) versus controls (0.2 ± 0.5 kg), with no significant differences between intervention groups (**Figure 1A**). Fat mass decreased (P < 0.05) in the 4-h and 6-h TRF groups, relative to controls. Lean mass was reduced (P < 0.05) in both TRF groups, versus controls, but greater reductions were noted by 6-h TRF. Visceral fat mass remained unchanged. Compliance with the TRF interventions was excellent. On average, participants in the 4-h TRF and 6-h TRF group reported being compliant with their feeding windows on 6.2 ± 0.2 d/week and 6.2 ± 0.1 d/week, respectively, during the 8-week trial (**Table 1**). Physical activity, measured as steps/day, did not change over the course of the trial in any group (**Table 1**).

Sleep measures

Results from the ISI survey indicates an absence of clinically significant insomnia in the 4-h TRF and control groups, but sub-threshold insomnia in the 6-h TRF group, at baseline (**Table 1**). After 8 weeks of diet, insomnia severity decreased (P < 0.05) in the 6-h TRF group only (Δ = -2.8 ± 1.0) versus controls (Δ = 0.4 ± 1.2) (**Figure 1B**). Thus, over the course of the trial, the 6-h TRF group went from displaying sub-threshold insomnia at baseline (8.3 ± 1.2) to no clinically significant insomnia post-treatment (5.5 ± 1.1). Sleep quality, timing, and duration was measured by the Pittsburgh Sleep Quality Index (PSQI). PSQI total score greater than 5 indicates poor sleep quality [99]. The average scores for PSQI were 5.9

$\pm$ 0.7 for 4-h TRF, 6.4 $\pm$ 0.8 for 6-h TRF and 6.7 $\pm$ 0.7 for controls, indicating poor sleep quality in all groups at baseline (**Table 1**). After 8 weeks of intervention, sleep quality scores did not change in either TRF group relative to controls (**Figure 1C**). Wake time, bedtime, and sleep duration did not change over the course of the study in any group (**Table 1**). Risk for obstructive sleep apnea was present in 44% of 4-h TRF subjects, 47% of 6-h TRF subjects and 46% of controls, at baseline (**Table 1**). By week 8, the risk of obstructive sleep apnea did not change in the 4-h or 6-h TRF groups, versus controls (**Figure 1D**).

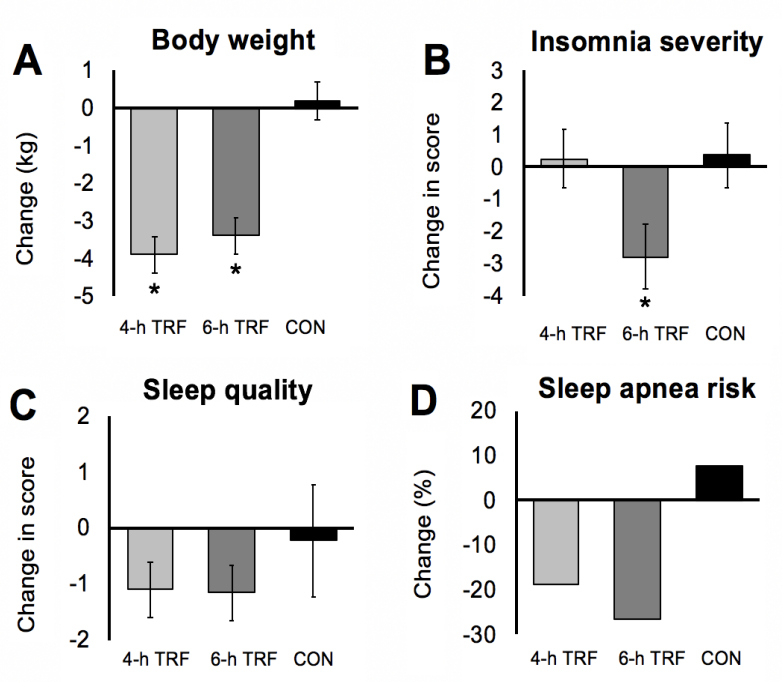


Figure 7. Change in body weight, insomnia severity, sleep quality and risk of obstructive sleep apnea

Continuous variables reported as mean ± SEM. Risk of obstructive sleep apnea reported as % occurrences. **A)** Body weight decreased similarly ($P < 0.001$) in the 4-h and 6-h TRF, versus controls. **B)** Insomnia severity decreased ($P < 0.05$) in the 6-h TRF group only versus controls. **C)** Sleep quality (PSQI) score did not change in the 4-h and 6-h TRF groups, versus controls. **D)** Risk of obstructive sleep apnea did not change in the 4-h and 6-h TRF groups versus controls.

Discussion

This study is the first to compare the effects of 4-h versus 6-h TRF on sleep in adults with obesity. We show here that 6-h TRF decreased insomnia severity after 8 weeks of diet. This effect, however, was not noted in the 4-h TRF group. We also assessed the impact of these TRF regimens on sleep quality, duration, or risk of obstructive sleep apnea. By the end of the study, none of these sleep parameters changed in either TRF group, relative to controls.

The goal of this exploratory analysis was to compare the effects of two popular forms of TRF (4-h versus 6-h TRF) on sleep. Weight loss has been shown to improve sleep in adults with obesity [42, 96, 97]. Since our original study [95] observed body weight reductions of ~3% with 4-h and 6-h TRF, we were interested in seeing if this degree of weight loss would improve sleep. After 8 weeks of intervention, sleep quality remained unchanged in both the 4-h and 6-h TRF groups. This finding is similar to what has been reported in other TRF studies. For instance, Gabel et al [7] observed no effect on sleep quality after 12 weeks of 8-h TRF, despite 3% weight loss. Wilkinson et al [8] also reported no change in sleep quality during 10-weeks of 10-h TRF, with 3% weight loss. There are several reasons that may explain why sleep quality was not affected by these fasting interventions. First, the weight loss observed by TRF is quite minimal (3-4% weight loss over 8-12 weeks [7] [8] [95]). It is possible that at least 5% weight loss may be necessary to see changes in sleep quality [41, 42]. Second, the participants in previous TRF studies were, for the most part, “good sleepers” at baseline (PSQI score <5 [99]). As such, it is not surprising that their sleep habits did not further improve by the end of the study. Sleep duration also did not change during either the 4-h or 6-h TRF intervention. However, our subjects had a mean sleep duration of ~7 h per night, which is in line with the 7 h minimum

recommended by the National Sleep Foundation [102]. Sleep duration also remained unaltered in the 8-h TRF study by Gabel et al [7] and the 9-h TRF study by Hutchison et al [13]. Risk of obstructive sleep apnea also did not change in the present study, relative to controls. The lack of a significant effect for this parameter was surprising as the percent of participants reporting sleep apnea decreased from ~40% to ~20% in both TRF groups by week 8. It is possible, however, that our study was underpowered to detect significant differences versus controls. Taken together, short-term 4-h and 6-h TRF do not improve sleep quality, sleep duration, or risk of obstructive sleep apnea in adults with obesity. A well powered clinical trial that specifically aims to assess the effect of TRF on various sleep parameters will be needed before solid conclusions can be reached.

Although most parameters of sleep remained unchanged in the present study, we did observe slight improvements in insomnia severity in the 6-h TRF group versus controls. Interestingly, these improvements were not observed by the 4-h TRF diet, despite similar weight loss. It should be noted however that *only* the 6-h TRF group displayed subthreshold insomnia at baseline (defined as an ISI score of 8-14 [98]). By the end of the study, participants in the 6-h TRF group reported no clinically significant insomnia (defined as an ISI score of 0-7 [98]). The reason why TRF may improve insomnia severity is uncertain. It has been postulated that fasting for at least 2-3 hours before bedtime may improve sleep [103]. Abstaining from eating (fatty and acidic foods in particular) before sleep may also help to reduce acid reflux and nighttime heartburn, which could contribute to lower rates of insomnia [104, 105]. In terms of future research, it will be of great interest to see if fasting interventions that limit food intake for at least 3 hours before bedtime can lessen insomnia severity in those afflicted by this condition.

Our study has several limitations. First, our sample size was small (n = 49). Since our power calculation was based exclusively on body weight, it is likely that this study was not powered adequately to identify significant changes in these sleep parameters. Second, all measures of sleep were assessed via self-report. This study would have benefitted from the use of wrist actigraphy to provide more objective assessments of rest and activity patterns. Third, we did not assess the choronobiology of our subjects at baseline. It would have been useful to implement the morningness–eveningness questionnaire (MEQ) [106] to quantify this important covariate.

In summary, these preliminary findings suggest that 4-h and 6-h TRF have very little impact on sleep quality, duration, or risk of obstructive sleep apnea. Insomnia severity, on the other hand, was improved slightly by the 6-h TRF diet. Although this study showed only minor positive effects on sleep, it is important to note that these fasting interventions did not negatively impact sleep by worsening sleep quality or shortening sleep duration. Thus, TRF can be viewed as an effective weight loss strategy that has no adverse impact on sleep in adults with obesity.

Authors' contributions

SC designed the research, conducted the clinical trial, analyzed the data, performed the statistical analysis, and wrote the manuscript; KG, FK, ME, VP, SL, and EW assisted with the conduction of the clinical trial; KAV designed the research, analyzed the data, and wrote the manuscript.

V. DISCUSSION

Aim 1: To compare the effects of 4-h versus 6-h time restricted feeding (TRF) on body weight and body composition in adults with obesity.

This is the first trial to examine the effect of 4-h versus 6-h TRF on body weight in adults with obesity. We show that 8 weeks of 4-h and 6-h TRF significantly decreases body weight by ~3% relative to the control group, with no difference between intervention groups. Thus, 4-h TRF does not produce superior changes in body weight compared to 6-h TRF, as hypothesized. Similar weight loss (~3%) was achieved with our previous trial implementing a larger eating window of 8-h TRF. However, the present study achieved ~3% weight loss in 10 weeks whereas our previous trial achieved ~3% weight loss in 12 weeks. Thus, shorter eating windows can potentially induce a faster rates of weight loss. There was a significant decrease in fat mass in both 4-h and 6-h TRF groups relative to controls. Lean mass decreased to a greater extent in the 6-h TRF group, versus the 4-h TRF group, and controls. Visceral fat mass remained unchanged in all groups. Very few studies have examined the weight loss efficacy of TRF in individuals with obesity [7, 8, 62]. In a recent trial of 8-h TRF, body weight was reduced by 2.6% after 12 weeks in men and women with obesity [7]. Likewise, 10-h TRF produced 3.6% weight loss after 16 weeks [62] and 3.0% weight loss after 12 weeks [8]. To our knowledge, no other study has examined the effect of 4-h or 6-h TRF as a weight loss regimen, thus, there is no data to which to compare our findings. In comparison with other forms of intermittent fasting, the degree of weight loss achieved with 4-h and 6-h TRF may be on par with that observed during short-term alternate day fasting (3-4 days of fasting per week) [3-5, 13, 14, 59] and the 5:2 diet (two days of fasting per week) [51, 55, 61].

TRF is a unique weight loss regimen in that it does not require calorie counting. Participants are simply asked to consume all their food for the day within a specified time frame, and water fast for the remaining hours of the day. We show here that by simply limiting the eating window to 4-h or 6-h, participants with obesity naturally decrease energy intake by ~550 kcal/d. From a clinical standpoint, these findings are paramount. One of the main reasons for participant attrition during daily CR and alternate day fasting trials is frustration with having to vigilantly monitor energy intake on a regular basis [4, 84, 85]. TRF regimens are able to side-step this requirement by allowing participants to simply watch the clock instead of monitoring calories, while still producing weight loss. Human trials of TRF with longer durations (>12 month) will be needed to see if these changes in energy intake persist long-term.

We also assessed changes in diet quality during TRF. It is conceivable that limiting the eating window to 4 or 6 hours per day could lead to the increased consumption of energy dense foods and compensatory drinking (i.e. increased diet soda and caffeine intake). As such, we examined whether key diet quality indicators, such as sugar, saturated fat, cholesterol, fiber and sodium intake, changed from baseline to week 8. Results reveal that changes in these parameters of diet quality by week 8 were not significantly different between the 4-h TRF, 6-h TRF, or control groups. Intakes of sugar, saturated fat, cholesterol, fiber and sodium were similar to what is typically consumed by the average American at baseline and post-treatment [91, 92]. In addition, changes in diet soda, sugar sweetened soda, caffeinated beverages excluding sodas (caffeinated coffee, caffeinated tea, energy drinks), or

alcohol intake by week 8 were not significantly different between the 4-h TRF, 6-h TRF, or control groups. Although the present short-term (8-week) trial shows no change in these key indicators of diet quality, these findings will need confirmation by a well-powered study that specifically examines the impact of 4-h and 6-h TRF on these parameters.

Aim 2: To compare the effects of 4-h versus 6-h TRF on metabolic disease risk factors in adults with obesity

This trial is the first to compare the effects of 4-h versus 6-h TRF on metabolic disease risk factors. Fasting insulin and insulin resistance were decreased similarly by both TRF interventions, versus controls. No change in fasting glucose was noted, which is similar to what has been reported previously by other intermittent fasting studies [12, 24, 32, 51, 60, 77]. Insulin and insulin resistance are routinely improved by TRF, alternate day fasting, and 5:2 [12, 24, 32, 51, 60, 77]. TRF has also been shown to improve beta-cell responsiveness in participants with prediabetes [32]. More recently, it was shown that intermittent fasting lowered insulin resistance *twice* as much as daily calorie restriction (CR), despite similar weight loss between the two intervention groups [24]. It should be noted, however, that the reductions in insulin and insulin resistance noted here are partly driven by a worsening in the control arm. It is questionable whether these improvements by TRF would have been noted in the absence of this. Our results are also limited in that we measured these glucoregulatory parameters only in the morning. Insulin sensitivity and glucose tolerance peak shortly after waking [65]. As such, future studies should measure these endpoints over a 24-h period (instead of the morning only) to see these regimens truly only impact insulin and insulin resistance, without concomitant changes in

glucose. One proposed mechanism by which fasting may improve glycemic control involves the metabolic switch. The metabolic switch, which occurs when changing from fed to fasted state, induces hepatocyte production of ketone bodies, increasing insulin sensitivity and decreasing fat accumulation. Insulin sensitivity of muscle cells is also enhanced in response to the metabolic switch [56].

Blood pressure did not change in either the 4-h TRF or 6-h TRF group versus controls. These findings are contrary to what has been reported previously. For instance, after 2-3 months of alternate day fasting or the 5:2 diet, systolic blood pressure is typically lowered by 5-8 mm Hg, while diastolic blood pressure is reduced by 3-5 mm Hg [19, 20, 23, 51, 58]. As for TRF, 6-h early TRF produced dramatic decreases in both systolic and diastolic blood pressure (-10-11 mm Hg) [32], while 8-h TRF has been shown to reduce systolic blood pressure (-7 mm Hg) [7], but not always [11]. It is unclear why blood pressure was not reduced by TRF in the present study. However, our study was not powered to see an effect in this secondary outcome variable.

Neither intervention had any effect on plasma lipid levels. The effects of intermittent fasting on plasma lipids are highly variable. While some studies report decreases in triglycerides and LDL cholesterol [18, 19, 23, 51], most show no effect on these lipid parameters [3, 7, 9, 20, 32, 58]. HDL also generally remains unaffected by these diets, though one study observed minor increases [4]. It should be noted, however, that the participants in the present study (and most previous studies) were not hypercholesterolemic. Since their baseline levels of LDL cholesterol and triglycerides were already in the normal range, it is not surprising that further reductions were not observed.

Aim 3: To compare the effects of 4-h versus 6-h time TRF on markers of inflammation and oxidative stress

There was a significant decrease in 8-isoprostane, a marker of oxidative stress to lipids, in both 4-h and 6-h TRF groups after 8 weeks, relative to controls. In contrast, neither intervention had any impact on inflammatory markers (circulating IL-6, or TNF-alpha). These reductions in oxidative stress are consistent with other human trials of intermittent fasting. In a 5-week trial of 6-h TRF, circulating 8-isoprostane was reduced by 14% in men with obesity and prediabetes, even without weight loss [32]. Correspondingly, 8-weeks of alternate day fasting decreased several markers of oxidative stress, including 8-isoprostane, 4-hydroxynonenal adducts, protein carbonyls, and nitrotyrosine [18]. As for inflammatory markers, human trials of intermittent fasting report no change in IL-6, TNF-alpha, or CRP [3, 9, 32, 34, 51]. Taken together, TRF along with other forms of fasting, have little effect on inflammation but have potent effects on oxidative stress. It is also likely that the decrease in oxidative stress noted here, is related to improvements in insulin resistance. Studies have demonstrated a clear link between insulin resistance and oxidative stress. Under oxidative conditions, insulin signaling is impaired, resulting in insulin resistance of the cell [81, 82]. Other studies have shown improvement in insulin sensitivity when administering antioxidants, such as vitamin E [83]. Therefore, we could speculate that one of the mechanisms by which intermittent fasting improves insulin resistance is by decreasing oxidative stress.Aim 4: To compare the effects of 4-h versus 6-h TRF on sleep quality and duration in adults with obesity

This study is the first to compare the effects of 4-h versus 6-h TRF on sleep in adults with obesity. We show here that 6-h TRF decreased insomnia severity after 8 weeks of diet. This effect, however, was not noted in the 4-h TRF group. We also assessed the impact of these TRF regimens on sleep quality,

duration, or risk of obstructive sleep apnea. By the end of the study, none of these sleep parameters changed in either TRF group, relative to controls. These preliminary findings suggest that 4-h and 6-h TRF have very little impact on sleep quality, duration, or risk of obstructive sleep apnea. Insomnia severity, on the other hand, was improved slightly by the 6-h TRF diet. Although this study showed only minor positive effects on sleep, it is important to note that these fasting interventions did not negatively impact sleep by worsening sleep quality or shortening sleep duration. Thus, TRF can be viewed as an effective weight loss strategy that has no adverse impact on sleep in adults with obesity.

VI. Future Directions

1. TRF for the management of PCOS: Polycystic ovary syndrome (PCOS) is one of the most common reproductive and endocrine disorders that affects up to 10% of women of childbearing age [107]. Abdominal adipose accumulation, insulin resistance, and low-grade chronic inflammation often co-occur with PCOS. Since up to 60% of women with PCOS are overweight or obese [108], guidelines recommend dietary and exercise interventions as first-line management in patients with PCOS [109]. Evidence has suggested that TRF can induce weight loss, ameliorate insulin resistance, and improve overall cardiometabolic health [110] [95]. One small pilot trial found that early TRF may be beneficial for treating anovulatory PCOS by improving menstruation, hyperandrogenemia, insulin resistance, and chronic inflammation [111]. However, more well-designed studies are needed to investigate the safety, applicability, and usefulness of TRF for PCOS patients.

2. TRF combined with different background diets: Future studies in this area should examine the effect of TRF combined with popular dietary patterns. Until now, TRF has only been studied with an ad libitum American diet, consisting of ~30% fat, 15% protein, 55% carbohydrates, and high amounts of processed foods and animal products. Concerns have been raised about individuals worsening their diet quality during shorter TRF eating windows, by increasing the consumption of ultra-processed foods and decreasing fiber and protein intake. It will be of interest to see if TRF combined with either a Paleo or low carbohydrate eating pattern could help to improve overall diet quality. It would also be of interest to see if these background diets combined with TRF would yield better results in terms of

weight loss and metabolic disease markers. Randomized controlled trials of TRF combined with the Mediterranean or Paleo eating pattern should be prioritized in future research.

3. TRF with early versus late eating windows: There is some new evidence showing that early TRF (eating all food before 3pm) may benefit metabolic health. For instance, in the study Sutton et al. [32] early 6-h TRF produced greater reductions in fasting insulin and insulin resistance in individuals with prediabetes versus a control diet (with no meal timing restrictions). It will be of interest for future research to *directly* compare the effects of early TRF (eating all food before 3pm) versus late TRF (eating all food after 3pm) to see if one diet produces superior weight loss and glucoregulatory effects. More studies examining how the timing of the eating window impacts metabolic parameters and diet compliance are desperately needed.

VII. Conclusion

Our study is the first randomized controlled trial to compare the weight loss efficacy of 4-h versus 6-h TRF in adults with obesity. Findings from this trial suggest that 4-h TRF does not produce superior weight loss or metabolic improvements versus 6-h TRF. Both fasting regimens induce mild reductions in body weight over 8 weeks (~3%), and show promise as interventions for weight loss. Reductions in insulin resistance and oxidative stress were also noted, which bode well for the use of these regimens in preventing cardiometabolic disease. Compliance was similar for 4-h and 6-h TRF, and both regimens reduced daily energy intake by ~550 kcal/d (30% reduction), without calorie counting. As for sleep,

neither 4-h or 6-h TRF had any significant effects on sleep quality or duration, suggesting that TRF may not disrupt sleep. Though these findings are promising, future trials will be needed to further examine the feasibility of TRF long-term, and also examine whether the weight loss and cardiometabolic benefits can be sustained over longer periods of time.

VIII APPENDICIES

APPENDIX A - CONSENT FORM

University of Illinois at Chicago
Research Information and Consent for Participation in Biomedical Research

Time restricted feeding (4-hour versus 6-hour) for weight loss in obese adults

You are being asked to participate in a research study. Researchers are required to provide a consent form such as this one to tell you about the research, to explain that taking part is voluntary, to describe the risks and benefits of participation, and to help you to make an informed decision. You should feel free to ask the researchers any questions you may have.

Principal Investigator Name and Title: Dr. Krista Varady, Ph.D., Associate Professor
Department and Institution: Kinesiology and Nutrition, University of Illinois at Chicago
Address and Contact Information: 1919 West Taylor Street, Room 532, Phone: 312-996-7897
Emergency Contact Name and Information: Krista Varady, Ph.D., Phone: 312-996-7897

Why am I being asked?

You are being asked to be a subject in a research study about time restricted feeding for weight loss. You have been asked to participate in the research because you responded to our ad and may be eligible to participate. Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future dealings with the University of Illinois at Chicago. **If you decide to participate, you are free to withdraw at any time without affecting that relationship.**

Approximately 150 subjects may be involved in this research at UIC.

What is the purpose of this research?

This research is being done to test the effects of time restricted feeding on weight loss and various diabetes and heart disease risk factors. Time restricted feeding is a diet that involves eating during a certain window of time each day. For instance, in this study, you will be asked to eat only from 1-7pm or 3-7pm (depending which group you are randomized to), and drink only water for the rest of the day.

What procedures are involved?

This research will be performed at the Human Nutrition Research Unit (HNRU), 1919 W Taylor St., Room 121C, in the Applied Health Sciences Building at UIC. You will need to come to the study site 10 times over the next 10 weeks. Each of those visits will take about 30-120 minutes.

The study procedures are:

Before you begin the main part of the study you will need to have the following "screening" tests or procedures to find out if you can be in the main part of the study.

- **Body weight assessment**: You will be weighed during the screening visit, and if you do not fall in the range of obese, you will not be eligible to participate.
- **Pregnancy screening:** If you are a premenopausal woman, you will be asked if you may be pregnant, and undergo a urine pregnancy test.
- **Alcohol intake assessment:** You will also complete a questionnaire to determine how much alcohol you drink per week.

If the screening exam shows that you can continue to be in the study, and you choose to take part, then you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

1. **4-hour Time restricted feeding group:** If you fall in this category you will be asked to consume food only between the hours of 3pm and 7pm each day. Before 3pm and after 7pm you will only be permitted to drink water.
2. **6-hour Time restricted feeding group:** If you fall in this category you will be asked to consume food only between the hours of 1pm and 7pm each day. Before 1pm and after 7pm you will only be permitted to drink water.
3. **Control group/ No treatment group:** If you fall in this category you will be asked not to change your diet in anyway. You will be asked to do this to better see if time restricted feeding has an effect in the two treatment groups.

You will take part in a study that is 10 weeks long (10 visits total) and at each visit you will be asked to do the following:

1. Week B1 visit: During your first visit, you will go to Human Nutrition Research Unit to:

- Have a blood draw (20 ml of blood, about 4 teaspoons)
- Have your blood pressure and body weight /percent fat/waist circumference measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Be given a food record, sleep habit, alcohol, and readiness for change questionnaires to fill out
- Be given an exercise monitor and instructed how and when to wear it

2. Week B2 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured

3. Week 1 visit:

- Have a blood draw (20 ml of blood, about 4 teaspoons)
- Have your blood pressure and body weight /percent fat/waist circumference measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Be given a food record, sleep habit, alcohol intake, readiness for change questionnaires to fill out
- Be given an exercise monitor and instructed how and when to wear it
- Be given dietary counseling to learn how to make general healthy choices and how to comply with the time restricted feeding diet (time restricted feeding groups only)

4. Week 2 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

5. Week 3 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

6. Week 4 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

7. Week 5 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

8. Week 6 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

9. Week 7 visit:

- Have your blood pressure and body weight /percent fat/waist circumference measured
- Be given dietary counseling to learn how to make general healthy choices (time restricted feeding groups only)

10. Week 8 visit:

- Have a blood draw (20 ml of blood, about 4 teaspoons)
- Have your blood pressure and body weight /percent fat/waist circumference measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Be given a food record, sleep habit, alcohol intake, readiness for change questionnaires to fill out
- Be given an exercise monitor and instructed how and when to wear it

What are the potential risks and discomforts?

The likely risks and discomforts expected in this study are:
1. Blood draw risk: Drawing blood may cause cause local pain, bruising, and more rarely, infection, light-headedness or fainting. A total of 60 ml of blood will be drawn during the study. All blood samples will be destroyed after the blood analyses are completed.
2. Time restricted feeding/reducing energy intake: Reducing daily energy intake has been shown to have beneficial effects on health. Studies of time restricted feeding have shown that it is generally well tolerated and has no harmful effects. You may feel hungry, however, which may be unpleasant.

3. Radiation exposure with X-ray scanning: The amount of radiation you will be exposed to during X-ray scanning is relatively small (equivalent to 10 days of normal daily radiation exposure). Radiation exposure can cause cell mutations that may lead to cancer. But the amount of radiation you're exposed to during an X-ray is so small that the risk of any damage to cells in your body is extremely low. If you have already had many x-rays, you should discuss this with the researchers before agreeing to be in the study.

What are the reproductive risks?

If you are a woman: Participating in this research may involve risks to pregnant women and/ or an unborn baby which are currently unforeseeable. To protect against possible side effects, if you are pregnant or nursing a child you may not take part in this study. If you are a woman of childbearing ability, you and the study doctor must either agree on a method of birth control to use or you must agree to be abstinent (i.e., not have sex) throughout the study. At every visit you will be asked if you are using acceptable method of birth control (e.g. low dose contraceptives, Nuvaring, Mirena IUD, Paragard IUD, barrier methods (such as condoms) combined with spermicide or diaphragm). If you think that you have become pregnant during the study, you must tell the doctor immediately. If you become pregnant, your participation will be stopped.

Will I be told about new information that may affect my decision to participate?

During the course of the study, you will be informed of any significant new research findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study may be re-obtained.

Are there benefits to taking part in the research?

If you are in the control group, you will not benefit from participation in this study. If you are assigned to a restricted feeding group, you may or may not benefit from participation in this study.

What other options are there?

If you decide not to enter this study, there is other care available to you, such as losing weight by reducing your daily energy intake on your own. The study coordinator will discuss this with you.

What about privacy and confidentiality?

The people who will know that you are a research subject are members of the research team, and if appropriate, your physicians and nurses. No information about you, or provided by you, during the research, will be disclosed to others without your written permission, except if necessary to protect your rights or welfare (for example, if you are injured and need emergency care or when the UIC Office for the Protection of Research Subjects monitors the research or consent process) or if required by law.

Study information which identifies you and the consent form signed by you will be looked at and/or copied for examining the research by:

- UIC Office for the Protection of Research Subjects, State of Illinois Auditors

A possible risk of the research is that your participation in the research or information about you and your health might become known to individuals outside the research. Your personal information and results will be kept as confidential as possible. To maintain confidentiality, code numbers only will identify all lab

specimens, evaluation forms, reports and other records. All records will be kept in locked files; code sheets linking your name to your identification number will be stored separately in a locked cabinet. Only study personnel will have access to the files. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity.

What if I am injured as a result of my participation?

If you get ill or injured from being in the study, UIC will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Krista Varady at the telephone number: 312-996-7897.

You should let any health care provider who treats you know that you are in a research study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact the research doctors.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study. Costs not covered by insurance could be substantial.

UIC has not set aside any money to pay you or to pay for your treatment if you get ill or injured from being in the study. There are no plans for the University to provide other forms of compensation (such as lost wages or pain and suffering) to you for research related illnesses or injuries. The only exception to this policy is if it is proven that your injury or illness is directly caused by the negligence of an UIC employee. By signing this form, you are not giving up any legal rights to seek compensation of injury.

What are the costs for participating in this research?

You will be required to pay for parking and travel expenses to the research center. However, you will not be required to pay for any of the study procedures, i.e. blood analysis, body scans, or dietary counseling sessions.

Will I be reimbursed for any of my expenses or paid for my participation in this research?

You will not be offered payment for being in this study. If you are randomized to the control group, you will receive 3 free weight loss dietary counseling sessions after you have completed the entire study.

Can I withdraw or be removed from the study?

If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without affecting your future care at UIC. You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the investigator may ask you to complete the final steps.

APPENDIX A - CONSENT FORM - (continued)

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest.
- You were to object to any future changes that may be made in the study plan.
- If you become ill during the research or you develop certain conditions during the study.
- If you don't follow the prescribed procedure.

Who should I contact if I have questions?

Contact the researchers Dr. Krista Varady (312-996-7897) or Sofia Cienfuegos (312-355-0542)

- If you have any questions about this study or your part in it,
- If you feel you have had a research-related injury (or a bad reaction to the study treatment), and/or
- If you have questions, concerns or complaints about the research.

What are my rights as a research subject?

If you have questions about your rights as a research subject or concerns, complaints, or to offer input you may call the Office for the Protection of Research Subjects (OPRS) at 312-996-1711 or 1-866-789-6215 (toll-free) or e-mail OPRS at uicirb@uic.edu.

What if I am a UIC employee?

Your participation in this research is in no way a part of your university duties, and your refusal to participate will not in any way affect your employment with the university, or the benefits, privileges, or opportunities associated with your employment at UIC. You will not be offered or receive any special consideration if you participate in this research.
Remember: Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

Signature of Subject

I have read (or someone has read to me) the above information. I have been given an opportunity to ask questions and my questions have been answered to my satisfaction. I agree to participate in this research. I will be given a copy of this signed and dated form.

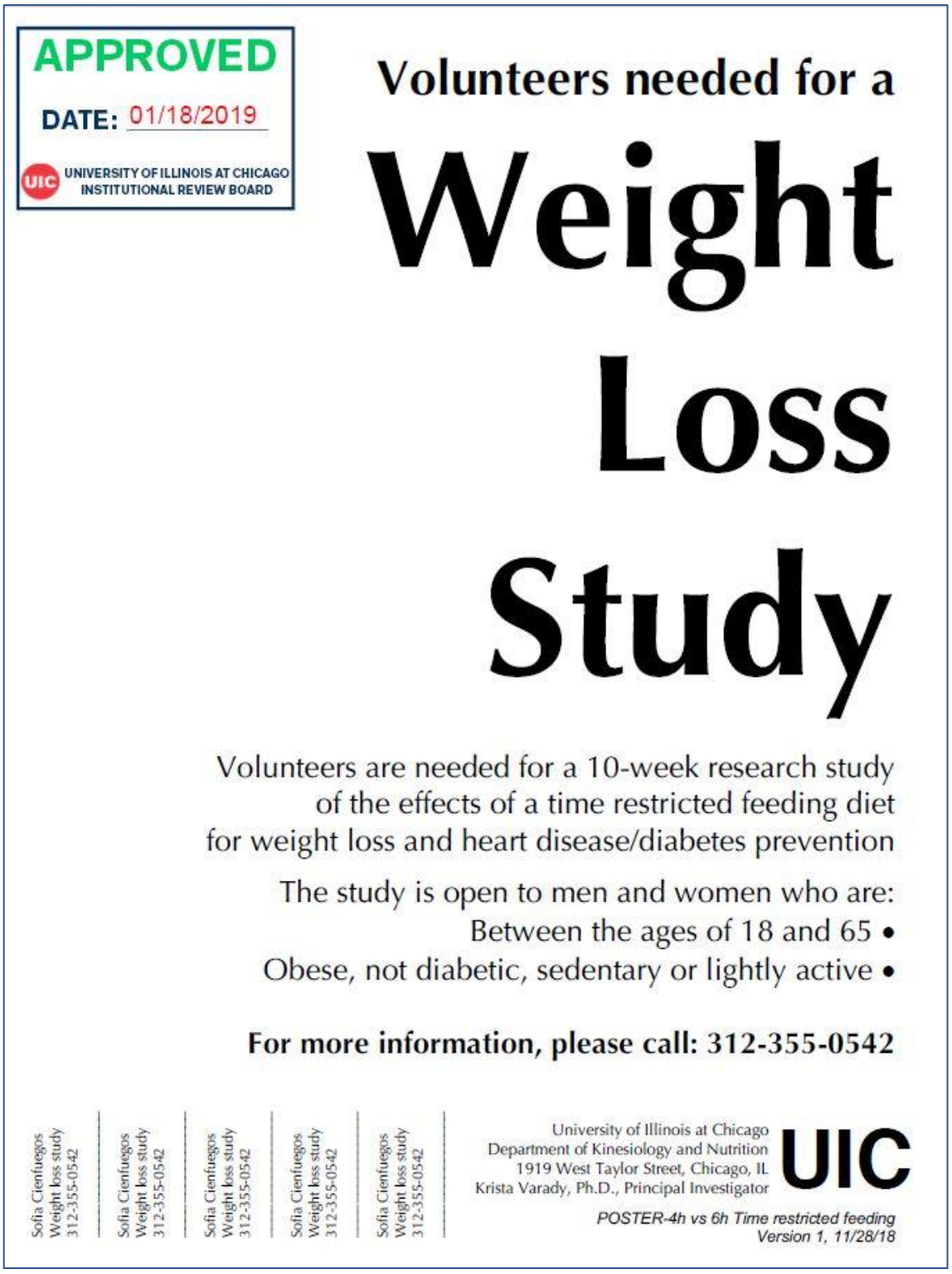
_____ _____
Signature Date

_____
Printed Name

_____ _____
Signature of Person Obtaining Consent Date (must be same as subject's)

_____
Printed Name of Person Obtaining Consent

APPENDIX B - RECRUITMENT POSTER



APPENDIX C – SCREENING QUESTIONNAIRE

Screening questionnaire

Subject ID: 019 –

Date of screening: _____

First name: _____ Middle initial: ____ Last: _____

Phone: _____ Email: _____

Age: _____ (Must be 18-65 yrs) DOB: _____ Sex: ☐ Female ☐ Male

Weight: _____ Height: _____ BMI: _____ (must be 30-49.9kg/m^2)

Ethnicity ☐ Hispanic/Latino ☐ Not Hispanic/Latino

Race ☐ American Indian ☐ Asian ☐ African American ☐ Native Hawaiian/Pacific Islander ☐ White

---

Do you smoke? ☐ yes ☐ no (If yes, disqualify)

Are you a night-shift worker? ☐ yes ☐ no (If yes, disqualify)

Currently Dieting? ☐ yes ☐ no (If yes, disqualify, not weight stable)

Weight gain/loss in past 3 months (>10 lb)? ☐ yes ☐ no (If yes, disqualify)

Can you commit to TRF for 10 weeks? ☐ yes ☐ no (If no, disqualify)

Do you exercise? ☐ yes ☐ no

Kind of exercise: _____ Total hours/week: _____

Do you have any health problems: ☐ yes ☐ no

If yes, explain: _____
(Disqualify if diabetic, history of eating disorders/binge eating)

Are you on any medications? ☐ yes ☐ no

Medication 1: _____

Medication 2: _____

Medication 3: _____

Medication 4: _____
(Must not be taking weight loss medications, or medication that requires eating food before (or with) the medication)

Peri-menopausal (3-6 missed periods in 12 mo)? ☐ yes ☐ no (If yes, disqualify)

Post-menopausal (absence of menses for > 2 y)? ☐ yes ☐ no

Pregnant or trying to become pregnant? ☐ yes ☐ no (If yes, disqualify)

4h versus 6h time restricted feeding
Version 1 – 11/28/18

APPENDIX D - TIME - RESTRCTED FEEDING INSTRUCTIONS

Time Restricted Feeding (TRF) diet guidelines **4-hour TRF GROUP**

WHEN can I eat each day?

- Start eating at 3pm each day (do not consume food before this time)
- Stop eating at 7pm each day (do not consume food after this time)

WHAT should I eat each day?

- You may eat whatever you like and whenever you like within this time frame (3pm to 7pm)
- There is no limitation on calories, fat, or carbohydrates with this diet, but try to implement the healthy eating tips that the Dietician discusses with you
- Alcohol is perimitted during this diet, but please limit intake to 2 alcholic beverages per day if you are a man, or 1 alcholic beverage per day if you are a woman

What can I consume during the non-eating period? (7pm to 3pm)

- Please DO NOT EAT ANY FOOD during this time frame
- Do not drink any beverages except those listed here:
  - Water as desired
  - Black coffee (without sugar, milk or cream)
  - Black tea or herbal tea (without sugar or milk)
  - Diet soda (please try to limit to 2 cans per day)
- You may also chew sugar-free chewing gum during this period

What forms do I need to complete each day?

- Use the "Timing of food intake log" each day to keep a record of when you start and stop eating (this will be reviewed at your weekly weigh-ins)
- Occasionally, the dietician will ask you to complete a 7-day food record to monitor your eating habits

Dietitian's Signature: _____ Date: _____

Subject signature: _____ Date: _____

APPENDIX D - TIME - RESTRCTED FEEDING INSTRUCTIONS (continued)

Time Restricted Feeding (TRF) diet guidelines **6-hour TRF GROUP**

WHEN can I eat each day?

- Start eating at 1pm each day (do not consume food before this time)
- Stop eating at 7pm each day (do not consume food after this time)

WHAT should I eat each day?

- You may eat whatever you like and whenever you like within this time frame (1pm to 7pm)
- There is no limitation on calories, fat, or carbohydrates with this diet, but try to implement the healthy eating tips that the Dietician discusses with you
- Alcohol is perimitted during this diet, but please limit intake to 2 alcholic beverages per day if you are a man, or 1 alcholic beverage per day if you are a woman

What can I consume during the non-eating period? (7pm to 1pm)

- Please DO NOT EAT ANY FOOD during this time frame
- Do not drink any beverages except those listed here:
  - Water as desired
  - Black coffee (without sugar, milk or cream)
  - Black tea or herbal tea (without sugar or milk)
  - Diet soda (please try to limit to 2 cans per day)
- You may also chew sugar-free chewing gum during this period

What forms do I need to complete each day?

- Use the "Timing of food intake log" each day to keep a record of when you start and stop eating (this will be reviewed at your weekly weigh-ins)
- Occasionally, the dietician will ask you to complete a 7-day food record to monitor your eating habits

Dietitian's Signature: _____ Date: _____

Subject signature: _____ Date: _____

APPENDIX E - FOOD RECORD

Food record instructions

1. Record everything you eat or drink (including plain water). This includes fruit juices, soft drinks, coffee (including any cream and sugar), and nutritional supplements such as Ensure or Boost.

2. Start a new page for each new day.

3. Try to record food items at the time you consume them. If you are away from home, you may want to record your food intake on a small note pad and transfer it to your food diary later.

4. If possible, measure your food with measuring cups, teaspoons, tablespoons and a ruler.

5. Obtain weights from package labels (snickers bar = 1.5 ounces or coke = 24 ounces).

6. If you are at a restaurant and cannot measure your food, estimate the amounts. If convenient, you may bring in food labels of foods consumed, such as candy wrappers and frozen entrée box labels.

7. Give as much detail as possible, for example:

    - 8 ounces non-fat milk, 10 ounces 2% milk, 12 ounces whole milk
    - 2 ounces cheddar cheese, jack cheese-3 in by 3 in by 1 in, 1 slice American cheese
    - 1 deep fried chicken thigh, 2 baked chicken breasts with marinara sauce
    - 8 ounce fried T-bone beef steak, 2 baked pork chops-3 ounces each
    - 1 slice whole wheat bread with 1 tsp of butter, 1 slice French bread from a bakery
    - 2 fried corn tortillas-6-inch diameter
    - 1 cup Dryers chocolate ice cream with 2 Tbsp. Hershey's chocolate sauce
    - 8 Oreo cookies, 2 homemade chocolate chip cookies-3 inch diameter
    - 2 scrambled eggs, cheese omelet made with 3 eggs, 1-ounce cheddar cheese, 1/2 cup spinach, 2 tsp. onions, and 1/4 cup mushrooms.
    - Salad made with 1 cup lettuce, 1 medium tomato, 1/2 medium avocado, and 4 Tbsp. Italian dressing
    - Sandwich made with 4 ounces turkey, 2 ounces jack cheese, 2 slices wheat bread, 2 teaspoons mayonnaise, 2 slices of tomato, and 1 piece of lettuce
    - 1 McDonald's Big Mac and medium order of fries
    - 4 tacos from Taco Bell
    - 1 large apple, 1/2 cup red grapes, 1 cup watermelon, 2 canned pear halves
    - 1 ounce potato chips, 12 ounces orange juice, 16 ounces fruit punch
    - 1 Walgreen's multi-vitamin pill

APPENDIX E - FOOD RECORD (Continued)

Time	Food Description	Amount

APPENDIX H – SLEEP SURVEY - INSOMNIA SEVERITY INDEX

Name: _____ *Date:* _____

Sleep Index

Please answer each of the questions below by circling the number that best describes your insomnia *in the past week.* Please answer all questions.

Please rate the current (past week's) **SEVERITY** of your insomnia problem(s):	None	Mild	Moderate	Severe	Very Severe
Difficulty falling asleep	0	1	2	3	4
Difficulty staying asleep	0	1	2	3	4
Problem waking up too early	0	1	2	3	4

How **SATISFIED/DISSATISFIED** are you With your current sleep pattern?	Very Satisfied	Mild	Moderate	Dissatisfied	Very Dissatisfied
	0	1	2	3	4

To what extent do you consider your sleep Problem to **INTERFERE** with your daily Functioning (eg, daytime fatigue, ability to Function at work/daily chores, concentration, Memory, mood, etc)?	Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
	0	1	2	3	4

How **NOTICABLE** to others do you think Your sleeping problem is in terms of Impairing the quality of your life?	Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
	0	1	2	3	4

How **WORRIED/DISTRESSED** are you about your current sleep problem?	Not at All worried	A Little	Somewhat	Much	Very Much Worried
	0	1	2	3	4

Total:	_____

\\ODO\odo_shared\PAT\Instructions\Recruiting\Briefing Qs\Sleep Index

APPENDIX I – SLEEP SURVEY - BERLIN SLEEP APNEA QUESTIONAIRE

RESMED

Berlin Questionnaire

SLEEP EVALUATION

Name _____ *Date* _____

1. Complete the following:

Height _____ Age _____

Weight _____ Male/Female _____

Has your weight changed?

- ☐ Increased
- ☐ Decreased
- ☐ No change

2. Do you snore?

☐ Yes ☐ No ☐ Don't know

If you snore:

3. Your snoring is...

- ☐ Slightly louder than breathing
- ☐ As loud as talking
- ☐ Louder than talking
- ☐ Very Loud

4. How often do you snore?

- ☐ Almost every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or almost never

5. Does your snoring bother other people?

☐ Yes ☐ No

6. Has anyone noticed that you quit breathing during your sleep?

- ☐ Almost every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or almost never

7. Are you tired after sleeping?

- ☐ Almost every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or almost never

8. Are you tired during waketime?

- ☐ Almost every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or almost never

9. Have you ever nodded off or fallen asleep while driving?

☐ Yes ☐ No ☐ Don't know

If yes, how often does it occur?

- ☐ Every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ Never or almost never

10. Do you have high blood pressure?

☐ Yes ☐ No ☐ Don't know

Patient Copy

APPENDIX J – SLEEP SURVEY - PITTSBOURGH SLEEP QUALITY INDEX (PSQI)

SLEEP INFORMATION

*Name:*_____ *Date:*_____

Instructions:
The following questions relate to your usual sleep habits during the past month *only*. Your answers should indicate the most accurate reply for the *majority* of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BED TIME_____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES_____
3. During the past month, when have you usually gotten up in the morning?
   USUAL GETTING UP TIME_____
4. During the past month, how many hours of *actual sleep* did you get at night? (This may be different than the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT_____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past month, how often have you had trouble sleeping because you…

a.	**Cannot get to sleep within 30 minutes**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
b.	**Wake up in the middle of the night or early morning**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
c.	**Have to get up to use the bathroom**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
d.	**Cannot breathe comfortably**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
e.	**Cough or snore loudly**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
f.	**Feel too cold**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
g.	**Feel too hot**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
h.	**Had bad dreams**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____
i.	**Have pain**			
	Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

APPENDIX J - PITTSBOURGH SLEEP QUALITY INDEX (PSQI) (continued)

j. **Other reason(s), please describe** _____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

6. During the past month, how would you rate your sleep quality overall?

Very good	_____
Fairly good	_____
Fairly bad	_____
Very bad	_____

7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all	_____
Only a very slight problem	_____
Somewhat of a problem	_____
A very big problem	_____

10. Do you have a bed partner or roommate?

No bed partner or roommate	_____
Partner/roommate in other room	_____
Partner in same room, but not same bed	_____
Partner in same bed	_____

In the last month, has anyone told you that you have had or do you recall that you have had…

a. Loud snoring

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

b. Long pauses between breaths while asleep

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

c. Legs twitching or jerking while you sleep

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

d. Episodes of disorientation or confusion during sleep

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

e. Other restlessness while you sleep; please describe _____

_____

Not during the Past month ____	Less than once a week ____	Once or twice a week ____	Three or more times a week ____

Please fill in the above questions (10 a-e) to the best of your knowledge.

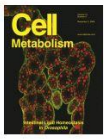
APPENDIX L - PEDOMETER LOG

Pedometer log – Step count record

Study number: _____ Subject ID: _____ Week: _____

Week	Day	Number of steps	What kind of exercise did you do today?
Date:	Mon		
Date:	Tue		
Date:	Wed		
Date:	Thur		
Date:	Fri		
Date:	Sat		
Date:	Sun		

APPENDIX M - COPYRIGHT AGREEMENT FOR MANUSCRIPT 1



Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity

Author: Sofia Cienfuegos,Kelsey Gabel,Faiza Kalam,Mark Ezpeleta,Eric Wiseman,Vasiliki Pavlou,Shuhao Lin,Manoela Lima Oliveira,Krista A. Varady

Publication: Cell Metabolism

Publisher: Elsevier

Date: 1 September 2020

APPENDIX N - COPYRIGHT AGREEMENT FOR MANUSCRIPT 2

Kirstyn Malcolm <Kirstyn.Malcolm@sagepub.co.uk> Wed, Jun 30, 3:36 AM (2 days ago)
to Craig, me, km

Dear Sofia and Craig,

Thank you for your email. You may use the Final Published PDF (or Original Submission or Accepted Manuscript, if preferred) in your dissertation or thesis (including where the dissertation or thesis will be posted in any electronic Institutional Repository or database) provided that access to the SAGE paper is provided at no charge and full citation is provided (ie, Cienfuegos S, Gabel K, Kalam F, et al. The effect of 4-h versus 6-h time restricted feeding on sleep quality, duration, insomnia severity and obstructive sleep apnea in adults with obesity. Nutrition and Health. March 2021. doi:10.1177/02601060211002347).

For more information on SAGE's author archiving and reuse guidelines, please see here: https://uk.sagepub.com/en-gb/eur/journal-author-archiving-policies-and-re-use

Please let me know if you have any further questions.

Best wishes,

Kirstyn Malcolm
Associate Editor, HSS/STM Journals
SAGE Publishing
1 Oliver's Yard, 55 City Road
London, EC1Y 1SP
UK

www.sagepublishing.com
SAGE Publishing is a trading name of SAGE Publications Ltd, Registered in England No.1017514

X. CITED LITERATURE

1. Stekovic, S., et al., *Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans.* Cell Metab, 2019. **30**(3): p. 462-476 e5.
2. Cho, A.R., et al., *Effects of alternate day fasting and exercise on cholesterol metabolism in overweight or obese adults: A pilot randomized controlled trial.* Metabolism, 2019. **93**: p. 52-60.
3. Bhutani, S., et al., *Alternate day fasting and endurance exercise combine to reduce body weight and favorably alter plasma lipids in obese humans.* Obesity (Silver Spring), 2013. **21**(7): p. 1370-9.
4. Trepanowski, J.F., et al., *Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults: A Randomized Clinical Trial.* JAMA Intern Med, 2017. **177**(7): p. 930-938.
5. Varady, K.A., et al., *Alternate day fasting for weight loss in normal weight and overweight subjects: a randomized controlled trial.* Nutr J, 2013. **12**(1): p. 146.
6. Coutinho, S.R., et al., *Compensatory mechanisms activated with intermittent energy restriction: A randomized control trial.* Clin Nutr, 2018. **37**(3): p. 815-823.
7. Gabel, K., et al., *Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study.* Nutr Healthy Aging, 2018. **4**(4): p. 345-353.
8. Wilkinson, M.J., et al., *Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome.* Cell Metab, 2020. **31**(1): p. 92-104 e5.
9. Moro, T., et al., *Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males.* J Transl Med, 2016. **14**(1): p. 290.
10. McAllister, M.J., et al., *Time-restricted feeding improves markers of cardiometabolic health in physically active college-age men: a 4-week randomized pre-post pilot study.* Nutr Res, 2019. **75**: p. 32-43.
11. Tinsley, G.M., et al., *Time-restricted feeding plus resistance training in active females: a randomized trial.* Am J Clin Nutr, 2019. **110**(3): p. 628-640.
12. Heilbronn, L.K., et al., *Glucose tolerance and skeletal muscle gene expression in response to alternate day fasting.* Obes Res, 2005. **13**(3): p. 574-81.
13. Hutchison, A.T., et al., *Effects of Intermittent Versus Continuous Energy Intakes on Insulin Sensitivity and Metabolic Risk in Women with Overweight.* Obesity (Silver Spring), 2019. **27**(1): p. 50-58.
14. Catenacci, V.A., et al., *A randomized pilot study comparing zero-calorie alternate-day fasting to daily caloric restriction in adults with obesity.* Obesity (Silver Spring), 2016. **24**(9): p. 1874-83.
15. Harder-Lauridsen, N.M., et al., *The effect of alternate-day caloric restriction on the metabolic consequences of 8 days of bed rest in healthy lean men: a randomized trial.* J Appl Physiol (1985), 2017. **122**(2): p. 230-241.
16. Hoddy, K.K., et al., *Changes in hunger and fullness in relation to gut peptides before and after 8 weeks of alternate day fasting.* Clin Nutr, 2016. **35**(6): p. 1380-1385.
17. Varady, K.A., et al., *Effects of weight loss via high fat vs. low fat alternate day fasting diets on free fatty acid profiles.* Sci Rep, 2015. **5**: p. 7561.
18. Johnson, J.B., et al., *Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma.* Free Radic Biol Med, 2007. **42**(5): p. 665-74.
19. Varady, K.A., et al., *Short-term modified alternate-day fasting: a novel dietary strategy for weight loss and cardioprotection in obese adults.* Am J Clin Nutr, 2009. **90**(5): p. 1138-43.
20. Hoddy, K.K., et al., *Meal timing during alternate day fasting: Impact on body weight and cardiovascular disease risk in obese adults.* Obesity (Silver Spring), 2014. **22**(12): p. 2524-31.

21. Klempel, M.C., C.M. Kroeger, and K.A. Varady, *Alternate day fasting increases LDL particle size independently of dietary fat content in obese humans.* Eur J Clin Nutr, 2013. **67**(7): p. 783-5.
22. Kalam, F., et al., *Alternate day fasting combined with a low-carbohydrate diet for weight loss, weight maintenance, and metabolic disease risk reduction.* Obes Sci Pract, 2019. **5**(6): p. 531-539.
23. Bowen, J., et al., *Randomized Trial of a High Protein, Partial Meal Replacement Program with or without Alternate Day Fasting: Similar Effects on Weight Loss, Retention Status, Nutritional, Metabolic, and Behavioral Outcomes.* Nutrients, 2018. **10**(9).
24. Gabel, K., et al., *Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance.* Obesity (Silver Spring), 2019. **27**(9): p. 1443-1450.
25. Arnason, T.G., M.W. Bowen, and K.D. Mansell, *Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study.* World J Diabetes, 2017. **8**(4): p. 154-164.
26. Tinsley, G.M., et al., *Time-restricted feeding in young men performing resistance training: A randomized controlled trial.* Eur J Sport Sci, 2017. **17**(2): p. 200-207.
27. Hutchison, A.T., et al., *Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial.* Obesity (Silver Spring), 2019. **27**(5): p. 724-732.
28. Kesztyus, D., et al., *Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design.* Nutrients, 2019. **11**(12).
29. Gabel, K., et al., *Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study.* Nutrition and healthy aging, 2018. **4**(4): p. 345-353.
30. Jamshed, H., et al., *Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans.* Nutrients, 2019. **11**(6).
31. Kahleova, H., et al., *Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study.* Diabetologia, 2014. **57**(8): p. 1552-60.
32. Sutton, E.F., et al., *Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes.* Cell Metab, 2018. **27**(6): p. 1212-1221 e3.
33. Carlson, O., et al., *Impact of reduced meal frequency without caloric restriction on glucose regulation in healthy, normal-weight middle-aged men and women.* Metabolism, 2007. **56**(12): p. 1729-34.
34. Trepanowski, J.F., et al., *Effects of alternate-day fasting or daily calorie restriction on body composition, fat distribution, and circulating adipokines: Secondary analysis of a randomized controlled trial.* Clin Nutr, 2018. **37**(6 Pt A): p. 1871-1878.
35. Liu, B., et al., *Markers of adipose tissue inflammation are transiently elevated during intermittent fasting in women who are overweight or obese.* Obes Res Clin Pract, 2019. **13**(4): p. 408-415.
36. Almeneessier, A.S. and A.S. BaHammam, *How does diurnal intermittent fasting impact sleep, daytime sleepiness, and markers of the biological clock? Current insights.* Nat Sci Sleep, 2018. **10**: p. 439-452.
37. Knutson, K.L., et al., *The National Sleep Foundation's Sleep Health Index.* Sleep Health, 2017. **3**(4): p. 234-240.
38. Beccuti, G. and S. Pannain, *Sleep and obesity.* Curr Opin Clin Nutr Metab Care, 2011. **14**(4): p. 402-12.
39. Hasler, G., et al., *The association between short sleep duration and obesity in young adults: a 13-year prospective study.* Sleep, 2004. **27**(4): p. 661-6.
40. Zimberg, I.Z., et al., *Short sleep duration and obesity: mechanisms and future perspectives.* Cell Biochem Funct, 2012. **30**(6): p. 524-9.
41. Alfaris, N., et al., *Effects of a 2-year behavioral weight loss intervention on sleep and mood in obese individuals treated in primary care practice.* Obesity (Silver Spring), 2015. **23**(3): p. 558-64.
42. Martin, C.K., et al., *Effect of Calorie Restriction on Mood, Quality of Life, Sleep, and Sexual Function in Healthy Nonobese Adults: The CALERIE 2 Randomized Clinical Trial.* JAMA Intern Med, 2016. **176**(6): p. 743-52.

43. Grandner, M.A., et al., *Criterion validity of the Pittsburgh Sleep Quality Index: Investigation in a non-clinical sample.* Sleep Biol Rhythms, 2006. **4**(2): p. 129-139.
44. Chaput, J.P., et al., *Psychobiological impact of a progressive weight loss program in obese men.* Physiol Behav, 2005. **86**(1-2): p. 224-32.
45. Verhoef, S.P., et al., *Concomitant changes in sleep duration and body weight and body composition during weight loss and 3-mo weight maintenance.* Am J Clin Nutr, 2013. **98**(1): p. 25-31.
46. Gill, S. and S. Panda, *A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits.* Cell metabolism, 2015. **22**(5): p. 789-798.
47. Gabel, K., et al., *Effect of 8-h time-restricted feeding on sleep quality and duration in adults with obesity.* Applied Physiology, Nutrition, and Metabolism, 2019. **44**(8): p. 903-906.
48. Stote, K.S., et al., *A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults.* The American journal of clinical nutrition, 2007. **85**(4): p. 981-988.
49. Gabel, K., K.K. Hoddy, and K.A. Varady, *Safety of 8-h time restricted feeding in adults with obesity.* Applied Physiology, Nutrition, and Metabolism, 2019. **44**(1): p. 107-109.
50. Akasheh, R.T., et al., *Weight loss efficacy of alternate day fasting versus daily calorie restriction in subjects with subclinical hypothyroidism: a secondary analysis.* Applied Physiology, Nutrition, and Metabolism, 2020. **45**(3): p. 340-343.
51. Harvie, M.N., et al., *The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women.* Int J Obes (Lond), 2011. **35**(5): p. 714-27.
52. Hoddy, K.K., et al., *Safety of alternate day fasting and effect on disordered eating behaviors.* Nutrition journal, 2015. **14**(1): p. 1-3.
53. Das, S.K., et al., *Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial.* The American journal of clinical nutrition, 2007. **85**(4): p. 1023-1030.
54. Williamson, D.A., et al., *Is caloric restriction associated with development of eating-disorder symptoms? Results from the CALERIE trial.* Health Psychology, 2008. **27**(1S): p. S32.
55. Sundfor, T.M., M. Svendsen, and S. Tonstad, *Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: A randomized 1-year trial.* Nutr Metab Cardiovasc Dis, 2018. **28**(7): p. 698-706.
56. de Cabo, R. and M.P. Mattson, *Effects of Intermittent Fasting on Health, Aging, and Disease.* N Engl J Med, 2019. **381**(26): p. 2541-2551.
57. Patterson, R.E. and D.D. Sears, *Metabolic Effects of Intermittent Fasting.* Annu Rev Nutr, 2017. **37**: p. 371-393.
58. Eshghinia, S. and F. Mohammadzadeh, *The effects of modified alternate-day fasting diet on weight loss and CAD risk factors in overweight and obese women.* J Diabetes Metab Disord, 2013. **12**(1): p. 4.
59. Klempel, M.C., C.M. Kroeger, and K.A. Varady, *Alternate day fasting (ADF) with a high-fat diet produces similar weight loss and cardio-protection as ADF with a low-fat diet.* Metabolism, 2013. **62**(1): p. 137-43.
60. Antoni, R., et al., *Intermittent v. continuous energy restriction: differential effects on postprandial glucose and lipid metabolism following matched weight loss in overweight/obese participants.* Br J Nutr, 2018. **119**(5): p. 507-516.
61. Schubel, R., et al., *Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial.* Am J Clin Nutr, 2018. **108**(5): p. 933-945.
62. Gill, S. and S. Panda, *A Smartphone App Reveals Erratic Diurnal Eating Patterns in Humans that Can Be Modulated for Health Benefits.* Cell Metab, 2015. **22**(5): p. 789-98.
63. Gabel, K., K.K. Hoddy, and K.A. Varady, *Safety of 8-h time restricted feeding in adults with obesity.* Appl Physiol Nutr Metab, 2019. **44**(1): p. 107-109.

64. Gabel, K., et al., *Effect of 8-h time-restricted feeding on sleep quality and duration in adults with obesity.* Appl Physiol Nutr Metab, 2019. **44**(8): p. 903-906.
65. Poggiogalle, E., H. Jamshed, and C.M. Peterson, *Circadian regulation of glucose, lipid, and energy metabolism in humans.* Metabolism, 2018. **84**: p. 11-27.
66. Morris, C.J., et al., *The Human Circadian System Has a Dominating Role in Causing the Morning/Evening Difference in Diet-Induced Thermogenesis.* Obesity (Silver Spring), 2015. **23**(10): p. 2053-8.
67. Scheer, F.A., et al., *Adverse metabolic and cardiovascular consequences of circadian misalignment.* Proc Natl Acad Sci U S A, 2009. **106**(11): p. 4453-8.
68. Nas, A., et al., *Impact of breakfast skipping compared with dinner skipping on regulation of energy balance and metabolic risk.* Am J Clin Nutr, 2017. **105**(6): p. 1351-1361.
69. Levitsky, D.A. and C.R. Pacanowski, *Effect of skipping breakfast on subsequent energy intake.* Physiol Behav, 2013. **119**: p. 9-16.
70. Geliebter, A., et al., *Skipping breakfast leads to weight loss but also elevated cholesterol compared with consuming daily breakfasts of oat porridge or frosted cornflakes in overweight individuals: a randomised controlled trial.* J Nutr Sci, 2014. **3**: p. e56.
71. Dhurandhar, E.J., et al., *The effectiveness of breakfast recommendations on weight loss: a randomized controlled trial.* Am J Clin Nutr, 2014. **100**(2): p. 507-13.
72. Sievert, K., et al., *Effect of breakfast on weight and energy intake: systematic review and meta-analysis of randomised controlled trials.* BMJ, 2019. **364**: p. l42.
73. Chowdhury, E.A., et al., *Six Weeks of Morning Fasting Causes Little Adaptation of Metabolic or Appetite Responses to Feeding in Adults with Obesity.* Obesity (Silver Spring), 2019. **27**(5): p. 813-821.
74. Antoni, R., Robertson TM, Robertson MD, Johnston JD., *A pilot feasibility study exploring the effects of a moderate time-restricted feeding intervention on energy intake, adiposity and metabolic physiology in free-living human subjects.* J Nutr Sci, 2018. **7**: p. 22.
75. Gayoso-Diz, P., et al., *Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study.* BMC Endocr Disord, 2013. **13**: p. 47.
76. Sumner, A.E. and C.C. Cowie, *Ethnic differences in the ability of triglyceride levels to identify insulin resistance.* Atherosclerosis, 2008. **196**(2): p. 696-703.
77. Hoddy, K.K., et al., *Effects of different degrees of insulin resistance on endothelial function in obese adults undergoing alternate day fasting.* Nutr Healthy Aging, 2016. **4**(1): p. 63-71.
78. Stote, K.S., et al., *A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults.* Am J Clin Nutr, 2007. **85**(4): p. 981-8.
79. Biston, P., et al., *Diurnal variations in cardiovascular function and glucose regulation in normotensive humans.* Hypertension, 1996. **28**(5): p. 863-71.
80. Persson, S.U., *Blood pressure reactions to insulin treatment in patients with type 2 diabetes.* Int J Angiol, 2007. **16**(4): p. 135-8.
81. Houstis, N., E.D. Rosen, and E.S. Lander, *Reactive oxygen species have a causal role in multiple forms of insulin resistance.* Nature, 2006. **440**(7086): p. 944-8.
82. Rains, J.L. and S.K. Jain, *Oxidative stress, insulin signaling, and diabetes.* Free Radic Biol Med, 2011. **50**(5): p. 567-75.
83. Zaulkffali, A.S., et al., *Vitamins D and E Stimulate the PI3K-AKT Signalling Pathway in Insulin-Resistant SK-N-SH Neuronal Cells.* Nutrients, 2019. **11**(10).
84. Dansinger, M.L., et al., *Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial.* JAMA, 2005. **293**(1): p. 43-53.
85. Das, S.K., et al., *Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial.* Am J Clin Nutr, 2007. **85**(4): p. 1023-30.

86. Redman, L.M., et al., *Effect of calorie restriction with or without exercise on body composition and fat distribution.* J Clin Endocrinol Metab, 2007. **92**(3): p. 865-72.
87. Ravussin, E., et al., *A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors of Health Span and Longevity.* J Gerontol A Biol Sci Med Sci, 2015. **70**(9): p. 1097-104.
88. Jimenez Jaime, T., et al., *Effect of calorie restriction on energy expenditure in overweight and obese adult women.* Nutr Hosp, 2015. **31**(6): p. 2428-36.
89. Goris, A.H., M.S. Westerterp-Plantenga, and K.R. Westerterp, *Undereating and underrecording of habitual food intake in obese men: selective underreporting of fat intake.* Am J Clin Nutr, 2000. **71**(1): p. 130-4.
90. Kretsch, M.J., A.K. Fong, and M.W. Green, *Behavioral and body size correlates of energy intake underreporting by obese and normal-weight women.* J Am Diet Assoc, 1999. **99**(3): p. 300-6; quiz 307-8.
91. Powell, E.S., L.P. Smith-Taillie, and B.M. Popkin, *Added Sugars Intake Across the Distribution of US Children and Adult Consumers: 1977-2012.* J Acad Nutr Diet, 2016. **116**(10): p. 1543-1550 e1.
92. Rehm, C.D., et al., *Dietary Intake Among US Adults, 1999-2012.* JAMA, 2016. **315**(23): p. 2542-53.
93. Morris, C.J., et al., *Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans.* Proc Natl Acad Sci U S A, 2015. **112**(17): p. E2225-34.
94. Williamson, D.A., G.A. Bray, and D.H. Ryan, *Is 5% weight loss a satisfactory criterion to define clinically significant weight loss?* Obesity (Silver Spring), 2015. **23**(12): p. 2319-20.
95. Cienfuegos, S., et al., *Effects of 4-and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity.* Cell metabolism, 2020. **32**(3): p. 366-378. e3.
96. Ashrafian, H., et al., *Bariatric Surgery or Non-Surgical Weight Loss for Obstructive Sleep Apnoea? A Systematic Review and Comparison of Meta-analyses.* Obes Surg, 2015. **25**(7): p. 1239-50.
97. Koren, D. and E.M. Taveras, *Association of sleep disturbances with obesity, insulin resistance and the metabolic syndrome.* Metabolism, 2018. **84**: p. 67-75.
98. Bastien, C.H., A. Vallieres, and C.M. Morin, *Validation of the Insomnia Severity Index as an outcome measure for insomnia research.* Sleep Med, 2001. **2**(4): p. 297-307.
99. Buysse, D.J., et al., *The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.* Psychiatry res, 1989. **28**(2): p. 193-213.
100. Chung, F., et al., *Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients.* Anesthesiology, 2008. **108**(5): p. 822-30.
101. Cienfuegos, S., Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Lima M, Varady KA, *Effects of four-hour and six-hour time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity* Cell Metabolism, 2020. **In press**.
102. Hirshkowitz, M., et al., *National Sleep Foundation's sleep time duration recommendations: methodology and results summary.* Sleep Health, 2015. **1**(1): p. 40-43.
103. Chaix, A., et al., *Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases.* Annu Rev Nutr, 2019. **39**: p. 291-315.
104. Lim, K.G., T.I. Morgenthaler, and D.A. Katzka, *Sleep and Nocturnal Gastroesophageal Reflux: An Update.* Chest, 2018. **154**(4): p. 963-971.
105. Surdea-Blaga, T., et al., *Food and Gastroesophageal Reflux Disease.* Curr Med Chem, 2019. **26**(19): p. 3497-3511.
106. Horne, J.A. and O. Ostberg, *A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms.* Int J Chronobiol, 1976. **4**(2): p. 97-110.
107. Bozdag, G., et al., *The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis.* Human Reproduction, 2016. **31**(12): p. 2841-2855.

108. Lim, S.S., et al., *Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis.* Human reproduction update, 2012. **18**(6): p. 618-637.
109. Teede, H.J., et al., *Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome.* Human reproduction, 2018. **33**(9): p. 1602-1618.
110. Cho, Y., et al., *The effectiveness of intermittent fasting to reduce body mass index and glucose metabolism: a systematic review and meta-analysis.* Journal of clinical medicine, 2019. **8**(10): p. 1645.
111. Li, C., et al., *Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome.* Journal of translational medicine, 2021. **19**(1): p. 1-9.

XI. VITA:

Sofia Cienfuegos, MS, RD
445 East Illinois St. Unit 6206. Chicago, Illinois. Zip 60611. USA.
Tel: (312) 622-6645, Email: sofia.cienfuegos@gmail.com

Education

PhD Human Nutrition	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2018 – Current **Thesis:** Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity **Supervisor:** Dr. Krista Varady, Ph.D.
MS Human Nutrition	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2016 – May 2018 **Supervisor:** Dr. Carol Braunschweig
B.S. Nutrition	**Universidad del Desarrollo – Facultad de Medicina UDD/CAS – Santiago, Chile** March 2009 – December 2013

Research Appointments

Clinical Coordinator	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** Supervisor: Dr. Krista Varady December 2018 – Current
Research assistant	**University of Illinois at Chicago – Institute for Health and Research Policy** Supervisor: Dr. Vanessa Oddo June 2020 – September 2020
Lab technician	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** Supervisor: Dr. Kelly Tappenden February 2018 – October 2018
Research assistant	**Rush University Medical Center** Supervisor: Dr. Carol Braunshweig April 2017 – February 2018

Teaching Appointments

Lecturer	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2018-Present Obesity (Graduate level), Vitamins and Minerals (Graduate level), Food and Culture (Undergraduate level).
Teaching Assistant	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2018 – Present

Food as Medicine (Undergraduate level), Foods (Undergraduate Level), Culture and Food Lab (Undergraduate level), science of foods (undergraduate level), Food service Management (undergraduate level).

Professional Positions

Clinical Dietitian	**CMMC Clinic –** Non-Pharmacological Treatment for Obesity 2015-2016 Nutrition therapy for patients enrolled in the obesity program.
Dietitian/Researcher	**SIP Network** 2014-2015 JAR School nutritional intervention project
Dietitian	**Nestle** 2015 Nutritional consultation in different regions of Chile and Santiago
Dietitian	**Private Practice** 2014-2017 Nutrition therapy, counseling, and management of chronic diseases.

Honors and Awards

2018	Achievement Award – University of Illinois at Chicago
2018	Kamath Award - University of Illinois, Chicago
2017	Golden Key Honor Society

Licenses and Certificates

2013-Present	Registered Dietitian Nutritionist – Santiago, Chile.
2014-Present	Integrative Coach – Impact Institute

Professional Affiliations

Member of the Academy of Nutrition and Dietetics since 2016
Member of the Obesity Society since 2018
Member of the American Society for Nutrition since 2017

Research Funding

ACTIVE

R01 DK119783, NIH (NIDDK) Varady (PI) 8/1/19 – 8/1/22
Alternate day fasting combined with exercise for the treatment of non-alcoholic fatty liver disease
The goal of this study was to compare the effects of a combination intervention (ADF and aerobic exercise) versus ADF or exercise alone versus a control on hepatic steatosis over 24-weeks in participants who are prediabetic, obese, and have been diagnosed with NAFLD.
Role: Clinical Coordinator

Publications

1. Lin S, Lima Oliveira M, Gabel K, Kalam F, **Cienfuegos S**, Ezpeleta M, Bhutani S, Varady KA. Does the weight loss efficacy of alternate day fasting differ according to sex and menopausal status? Nutr Metab Cardiovasc Dis. 2020 Oct 31:S0939-4753(20)30457-9.

2. **Cienfuegos S**, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Oliveira ML, Varady KA. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Cell Metab. 2020 Sep 1;32(3):366-378.e3.

3. Gabel K, Marcell J, Cares K, Kalam F, **Cienfuegos S**, Ezpeleta M, Varady KA. Effect of time restricted feeding on the gut microbiome in adults with obesity: A pilot study. Nutr Health. 2020 Jun;26(2):79-85.

4. McKeever L, Peterson SJ, **Cienfuegos S**, Rizzie J, Lateef O, Freels S, Braunschweig CA. Real-Time Energy Exposure Is Associated With Increased Oxidative Stress Among Feeding-Tolerant Critically Ill Patients: Results From the FEDOX Trial. JPEN J Parenter Enteral Nutr. 2020 Nov;44(8):1484-1491.

5. Kalam F, Gabel K, **Cienfuegos S**, Wiseman E, Ezpeleta M, Steward M, Pavlou V, Varady KA. Alternate day fasting combined with a low-carbohydrate diet for weight loss, weight maintenance, and metabolic disease risk reduction. Obes Sci Pract. 2019 Sep 13;5(6):531-539.

6. Akasheh RT, Kroeger CM, Trepanowski JF, Gabel K, Hoddy KK, Kalam F, **Cienfuegos S**, Varady KA. Weight loss efficacy of alternate day fasting versus daily calorie restriction in subjects with subclinical hypothyroidism: a secondary analysis. Appl Physiol Nutr Metab. 2020 Mar;45(3):340-343.

7. Gabel K, Kroeger CM, Trepanowski JF, Hoddy KK, **Cienfuegos S**, Kalam F, Varady KA. Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance. Obesity (Silver Spring). 2019 Sep;27(9):1443-1450.

8. Kalam F, Kroeger CM, Trepanowski JF, Gabel K, Song JH, **Cienfuegos S**, Varady KA. Beverage intake during alternate-day fasting: Relationship to energy intake and body weight. Nutr Health. 2019 Sep;25(3):167-171.

Abstracts

1. **Cienfuegos S**, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Lima Oliveira M, Varady KA. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Obesity Week 2019, Las Vegas NV, 2019 [Poster Presentation]

2. **Cienfuegos S**, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Lima Oliveira M, Varady KA. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Overcoming Obesity 2020 [poster presentation]

3. **Cienfuegos S**, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V, Lin S, Lima Oliveira M, Varady KA. The effect of 4-h versus 6-h time restricted feeding on sleep quality, insomnia severity and obstructive sleep apnea in adults with obesity. Obesity Week 2020 [poster presentation]

Invited Talks

1. Cienfuegos S "Effect of Time Restricted Feeding on Weight Loss and Cardiometabolic Health" The physiological society. Physiology of Obesity, 2020 [Invited speaker]

2. Cienfuegos S "Intermittent fasting for weight loss and metabolic health" Revision Critica, Mexico City 2020 [Invited Speaker]

3. Cienfuegos s "Time Restricted Feeding and Obesity" The Physiology Forum 2020 [Podcast invited speaker]

Media Attention

Eurek Alert	How long should you fast for weight loss?	2020
Scientific American	How Good a Diet Is Intermittent Fasting?	2020
Endocrinology Network	Time-Restricted Diets Effective for Losing Weight	2020
The New York Times	Intermittent Fasting May Aid Weight Loss	2020
Earth.com	Fasting diets are effective for weight loss	2020