Effect of Time Restricted Feeding on Body Weight

Metabolic Disease Risk Factors in Adults with Obesity

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THESIS

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KNDG

CONTRIBUTION OF AUTHORS

Chapter 1 gives a brief background of intermittent fasting including the rationale, specific aims and significance of my research question.

Chapter 2 is a literature review of the current published studies in the field of fasting. This chapter highlights the significance and rationale behind my research question.

Chapter 3 represents a published manuscript on the primary outcomes of my research question. I was the first author. Kristin K Hoddy, Cynthia Kroeger, John F Trepanowski, Nicole Haggerty, and Jeehee Song helped with the conduction of the clinical trial. Dr. Satchin Panda helped with data analysis. My research mentor, Dr. Krista A Varady helped write the manuscript.

Chapter 4 represents a published manuscript on secondary outcomes of my research question. I was the first author of this manuscript and the primary author. Kristin K Hoddy helped with the conduction of the trial and data analysis. My research mentor Dr. Varady helped with trial design and editing the manuscript.

Chapter 5 represents a published manuscript on secondary outcomes of my research question. I was the first author for this manuscript and the primary author. Kristin K Hoddy helped in the conduction of the clinical trial. Dr Helen Burgess helped with the data analysis and sleep measurements. My research mentor Dr. Varady helped with the trial design and editing the manuscript.

Chapter 6 gives a summary of my research findings in response to each specific aim.

Chapter 7 describes future directions that should be explored in time restricted feeding.

Chapter 8 represents the summary of the research findings described in my dissertation as well my predominant conclusions.

Chapters 9-11 are comprised of appendices including the copyright agreement for each previously published manuscript, cited literature and my curriculum vitae.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADF	Alternate day fasting
BMI	Body mass index
BSQ	Body shape questionnaire
CHD	Coronary heart disease
CR	Calorie Restriction
CVD	Cardiovascular disease
DIO	Diet induced obesity
HDL	High-density lipoprotein
IR	Insulin Resistance
ISI	Insomnia Sleep Index
LDL	Low-density Lipoprotein
MEADS	Multi-dimensional assessment of eating disorder symptoms
PSQI	Pittsburg Sleep Quality Index
RMR	Resting metabolic rate
SEM	Standard error or mean
T2DM	Type Two Diabetes Meletus
TFEQ	Three Factor Eating Questionnaire
TRF	Time-restricted feeding
WC	Waist circumference

SUMMARY

This study investigated the effects of time restricted feeding (TRF) on body weight, metabolic disease risk factors, and sleep in adults with obesity. The safety of TRF was also evaluated. TRF is a form of intermittent fasting that requires individuals to eat all their food within a certain window of time each day, and water fast for the remaining hours of the day. Obese subjects (n = 23) participated in an 8-h time restricted feeding intervention (ad libitum feeding between 10:00 to 18:00 h, water fasting between 18:00 to 10:00 h) for 12 weeks. Results from this study show that 12 weeks of 8-h TRF decreases body weight by ~3%. Subjects were adherent to the prescribed eating window on ~6 days per week, and this level of adherence remained constant throughout the 12-week trial. Our findings also indicate that reducing the daily eating window to 8-h/d decreases caloric intake by ~300 kcal/d, without intentional calorie counting. TRF produced significant reductions in systolic blood pressure, however, other metabolic disease risk parameters (plasma lipids and glucoregulatory factors) remained unchanged. TRF had no effect on sleep quality, timing, duration, or insomnia severity after 12 weeks. Our results also suggest that TRF is a safe diet therapy that does not negatively affect eating disorder symptoms, eating behaviors, or measures of overall health such as resting metabolic rate and complete blood count. These preliminary data offer promise for the use of TRF as a safe weight-loss technique in adults with obesity, but longer-term, larger-scale randomized controlled trials will be required before solid conclusions can be reached.

I. INTRODUCTION

1. Background and Rationale:

Obesity increases the risk of metabolic disease [1]. Excess fat is associated with dyslipidemia, hypertension, and insulin resistance [1]. As little as 5% weight loss has been shown to improve these metabolic parameters, thereby decreasing risk of disease [2]. Intermittent fasting is a novel diet for weight loss and the improvement of metabolic disease risk factors. Alternate day fasting (ADF) and the 5:2 diet are the most studied forms of intermittent fasting. ADF consists of a "fast" day where a person consumes ~500 kcal (~25% of calorie needs), alternated with a "feed" day of ad libitum eating. In contrast, the 5:2 diet includes two fast days per week (~500 kcal) followed by 5 days of ad libitum eating. Recent human research has shown a weight loss of 3-13% after 4-24 weeks of ADF and the 5:2 diet [3-13]. This weight loss has beneficial effects on blood pressure, triglycerides, LDL cholesterol, and insulin [3-13]. However, counting calories and fasting every other day may still inhibit adherence and decrease success with 5:2 and ADF [3].

Time-restricted feeding (TRF) is the newest form of intermittent fasting, but little research has been done in this area. TRF requires individuals to eat all their food within a certain window of time each day, and water fast for the remaining hours of the day. The most common form of TRF is the 8-h eating window, also called "8-h TRF". During the 8-h eating window (e.g. 10:00 to 18:00 h), food intake is ad libitum and participants are not required to count calories. During the fasting window (e.g. 18:00 to 10:00) subjects are only permitted water and calorie-free beverages.

It is speculated that TRF may naturally decrease caloric intake simply by watching a clock daily rather than counting calories or fasting every other day. Currently, nearly all TRF research has been conducted in rodent models during adolescence or after diet induced obesity (DIO). Mice fed an isocaloric diet during the 12-h dark phase (their normal circadian feast phase) weighed 19% less than those fed during the light phase. Those fed during the light phase also had increased body fat compared to their circadian timed counterparts, however this was not significant [14]. Chaix et al [15] examined different lengths of TRF in relation to high-fat, high-fructose and normal diets. Their group observed that 9-h, 12-h, and 15-h TRF seemed to limit DIO caused by a high-fat diet. TRF also appeared to be beneficial after DIO had already occurred [15]. TRF rodent models show that 9-h to 16-h of fasting, even under isocaloric conditions, resulted in decreased weight and body-fat mass in both high-fat and low-fat diets [15-20].

Humans, like mice, have diurnal circadian clocks. Due to this similarity, it has been speculated that TRF may also positively effect body weight and body composition in humans. Only five human trials of TRF have been conducted to date [21-25]. Gill and Panda [21] examined the effects of 10-h TRF in healthy adults with overweight and resulted in a 4% weight loss that was sustained for one year. Findings from two other studies in young, lean, resistance-trained men revealed that 4-8-h TRF reduces caloric intake (without calorie counting) and significantly decreases fat mass while maintaining lean mass [22, 23]. Sutton et al [24] examined the effect of early time-restricted feeding (8:00-14:00) on metabolic disease risk factors independent of weight loss in 8 pre-diabetic men. This group observed improvements in blood pressure, mean insulin, insulin after a meal, and beta-cell responsiveness [24]. Arnason et al [25] also ran a pilot trial on the effect of TRF on metabolic disease risk factors in individuals with type-2

diabetes. They observed significant weight loss, decreased post-prandial glucose variability, improved glucose control, and more subjects achieved their fasting morning glucose goal after the intervention [25]. **However, there have been no studies evaluating the effects of 8-h TRF on body weight and metabolic disease risk factors in subjects with *obesity*.**

Gill and Panda [21] recently examined real-time eating patterns in in 156 adults utilizing a smart-phone application. This group found that subjects had a mean eating duration of 14-h+ per day [21]. It is possible that decreasing this window may naturally restrict calories or may have the same metabolic health benefits as seen in rodent models [14, 15, 18]. Gill and Panda [21] also observed that calories ingested after 18:00 h exceeded calorie needs for weight maintenance. Furthermore, many commercially available weight loss books have touted the benefits of 8-h TRF however, no research has been done in humans at this eating/fasting interval. We chose to implement an 8-h TRF window due to this lack of evidence. **We chose to place the 8-h TRF feeding window from 10:00 to 18:00 h in order to allow for a 3 meal/day eating pattern as well as to end eating at 18:00 h when calorie needs have been met.**

Due to the novelty of TRF, the safety of the diet has not yet been evaluated. Fasting interventions often raise concerns regarding gastrointestinal disturbances, problems with blood sugar regulation, or disturbances in resting metabolic rate. Intermittent fasting regimens had also been speculated to increase disordered eating behaviors and negatively impact body image perception, however this was not observed in a previous ADF study [26]. **The occurrence of adverse events, changes in eating**

disorder symptoms and alterations in body image perception has yet to be examined in any TRF study to date.

Obesity is associated with poor sleep quality, shorter sleep duration, and increased risk of sleep apnea [27-29]. Weight loss as a result of dietary restriction may improve sleep quality and quantity. In a 10-h TRF intervention Gill and Panda [21] observed improved sleep via self-report in subjects. **The effect of 8-h TRF on sleep has yet to be examined.**

Therefore, the specific aims of the study are as follows:

2. Specific Aims

Specific Aim 1: To examine the effects of 8-h TRF on **body weight and body composition** in adults with obesity.

Hypothesis 1: Body weight, fat mass, and visceral fat mass will decrease after 12 weeks of 8-h TRF in adults with obesity. Lean mass will remain unchanged.

Specific Aim 2: To examine the effects of 8-h TRF on **metabolic disease risk factors** in adults with obesity.

Hypothesis 2: Fasting insulin, glucose, insulin resistance (measured by HOMA-IR), HbA1c, triglycerides, and blood pressure will be reduced after 12 weeks of 8-h TRF in adults with obesity.

Specific Aim 3: To examine the effects of 8-h TRF on **sleep quality and duration** in adults with obesity.

Hypothesis 3: Self-reported sleep quality and duration will increase after 12 weeks of 8-h TRF in adults with obesity.

Specific Aim 4: To evaluate the **safety** of 8-h TRF in adults with obesity.

Hypothesis 4: Eating disorder symptoms, body image perception, complete blood count, and frequency of adverse events will remain unchanged after 12 weeks of 8-h TRF in adults with obesity.

3. Significance

If the aims of this application are achieved, this study will:

1. Improve clinical guidelines by showing that TRF is effective for reducing body weight and improving metabolic disease risk factors (plasma lipids, fasting glucose, insulin, and insulin resistance) in obese adults.
2. Further the field's understanding of fasting on sleep quantity and quality.
3. Report the safety of TRF with regards to adverse events, eating disorder symptoms, and body image.

II. LITERATURE REVIEW

1. Obesity and metabolic disease risk

One-hundred sixty million Americans are either overweight or obese [30]. This puts the United States in the top 15 countries with the highest rates of obesity [30]. Obesity can lead to increased inflammatory cytokines resulting in a cascade of health effects including increased risk of insulin resistance, cardiovascular disease, and type 2 diabetes. Recent evidence shows that as little as 5% weight loss can decrease the risk of these obesity-related comorbidities [2].

Calorie restriction (CR) is the most common treatment used to facilitate weight loss. However, adherence to CR declines after the first month of intervention and continues to decrease thereafter [3]. Intermittent fasting is an alternative to CR that utilizes extended times of fasting to decrease daily caloric intake. The most well-known forms of intermittent fasting are alternate day fasting (ADF), the 5:2 diet, and the 6:1 diet. ADF consists of a “fast” day where a person consumes ~500 kcal (~25% of calorie needs), alternated with a “feed” day of ad libitum eating. In contrast, the 5:2 diet includes two fast days per week (~500 kcal) followed by 5 days of ad libitum eating, while the 6:1 diet includes only one fast day per week (~500 kcal), followed 6 days of ad libitum eating.

Time restricted feeding (TRF) is the newest form of intermittent fasting. TRF requires individuals to eat all food within a certain window of time each day, and water fast for the remaining hours of the day. The most common form of TRF is the 8-h eating window, also called “8-h TRF”. During the 8-h eating window (e.g. 10:00 to 18:00 h), food intake is ad libitum and participants are not required to count

calories. During the fasting window (e.g. 18:00 to 10:00 h) subjects are only permitted water and calorie-free beverages.

This literature review summarizes the effects of these various IF approaches (ADF, 5:2, 6:1, and TRF) on body weight, body composition, metabolic disease risk factors, and sleep. The safety of these regimens will also be reviewed.

2. Effect of intermittent fasting on body weight and body composition

To date, 18 studies have examined the effect of the 6:1 diet, 5:2 diet, or ADF on body weight and body composition [3-13, 31-38]. Results of these studies are summarized in **Table 1**. Five studies have specifically examined the effect of TRF on body weight and body composition [21-25]. For the purpose of this review three studies examining the effect of meal frequency and one study examining the effect of five days of CR with 2 days of Ramadan-style fasting will be included in the TRF analysis as they might point to the effect of a shortened feeding window on body weight, body composition, and metabolic risk factors [39-42]. These TRF findings are displayed in **Table 2.**

2.1 Intermittent fasting effect on body weight

5:2 and 6:1

In a study by Kessler et al [31], subjects were randomized to a 6:1 diet or a no-intervention control group. After 8 weeks of this diet, body weight remained unchanged. Zuo et al [32] also examined the short-term effects of the 6:1 diet on body weight. After 12 weeks of fasting 1 day per week combined with 6 days of CR, body weight was significantly reduced by 10% [32]. As for the 5:2 diet, Harvie et al

[4] and Sundfør et al [13] both observed significant weight loss (5-8%) on the 5:2 diet after 24 weeks. Carter et al [5, 6] also observed significant weight loss (6%) with the 5:2 diet, however, this group did ask participants to increase physical activity which may overstate these outcomes .

ADF

Three trials have looked at the effect of short-term (<8 weeks) ADF interventions on body weight [7, 33, 34]. Results reveal that 2 weeks of ADF does not significantly decrease body weight [33, 34]. However, when the diet was followed for a slightly longer period of time (3 weeks), Heilbronn et al [7] demonstrated a significant 3% weight loss. Six moderate-term studies (8-12 weeks) have examined the effect of ADF on body weight [8-10, 12, 36, 37, 43]. All 8-week studies observed significant weight loss of 4-9% from baseline [8-10, 12, 36, 37, 43]. Three studies have evaluated the effect of long-term (>12 weeks) ADF on body weight [3, 11, 38]. Varady et al [11], Coutinho et al [38], and Trepanowski et al [3] observed weight loss of 7-13% after 12- 24 weeks. Thus, ADF appears to be an effective weight loss intervention when applied for >3 weeks.

TRF

Four studies examined the effect of ≤4-h TRF on body weight [23, 25, 39, 40] (**Table 2**). Arnason et al [25] observed a significant weight loss of 1.5% after 2 weeks of 4-6-h TRF in subjects with diabetes. Stote et al [40] and Carlson et al [39] evaluated 1 meal/day with a 4-h feeding window versus 3 meals/day in a randomized crossover trial. Calories were set for weight maintenance for both the 1 meal and 3 meals per day groups. However, only subjects in the 1 meal/day group lost 2% body weight after 8 weeks [39, 40]. Tinsley et al [23] also examined 4-h TRF, however, TRF was only implemented 4

days/week and calories were set for weight maintenance. Tinsley et al [23] did not observe significant weight loss, yet it is important to note that subjects ate almost 670 kcals less on the days of the TRF intervention. This natural decrease in caloric intake is promising for TRF if subjects are left to eat ad-libitum. Five studies also looked at effect of >4-h TRF on body weight [21, 22, 24, 41, 42]. Kahelova et al [41] examined a 10-h feeding window (2 meals/day) versus 6 meals per day. The 10-h TRF diet resulted in significant weight loss despite caloric intake prescribed at maintenance [41]. Conversely, Moro et al [22] and Sutton et al [24] demonstrated no change in body weight after 8-h TRF in lean resistance-trained men or 6-h TRF in pre-diabetic men with overweight or obesity, respectively. In both trials, calories were set for weight maintenance [22, 24]. Gill and Panda [21] is the only group to examine ad-libitum >6-h TRF. This group observed a 4% weight loss after instructing overweight subjects to eat in a 10-12-h TRF window (eating window at baseline was >14-h/d) [21]. These preliminary data suggest that TRF diets produce mild weight loss (1-4%) over 2-16 weeks in normal weight and overweight adults. The effects of TRF on body weight in obese subjects remains unknown.

2.2 Body composition

2.2.1 Fat mass

6:1, 5:2 and ADF

Kessler et al [31], Carter et al [5, 6], and Harvie et al [4] observed significant decreases in fat mass after a 6:1 or 5:2 intervention. As for ADF, interventions less than two weeks appear to have no effect on fat mass [33, 34]. However, three weeks of ADF significantly decreased fat mass [7]. All ADF interventions lasting 8 weeks significantly decreased fat mass [2, 8-10, 36, 37, 44]. Similarly, three studies of long-term ADF (>12 weeks) also all resulted in significant fat mass loss [3, 11, 38].

Table 1: Effects of 6:1, 5: 2, and ADF on body weight and body composition

Reference	Subjects	Design	Intervention	Length (weeks)	Body weight	Fat mass	Fat-free mass	Visceral fat mass
6:1 diet								
Kessler et al [31]	36	non-randomized control	6: 1d fast vs control	8 wks	Ø	↓	↓	Ø
Zuo et al [32]	40 overweight and obese	single cohort	6CR: 1 fast	12 wks	↓10%	-	-	-
5:2 diet								
Carter et al [5]	63 T2DM	randomized	5:2 vs CR	12 wks	↓6%	↓	↓	-
Sundfør et al [13]	112 obese	randomized	5:2 vs CR	24 wks	↓8%	-	-	-
Harvie et al [4]	107 women	randomized	5:2 vs CR	24 wks	↓5%	↓	↓	↓ WC
Carter et al[6]	137 T2DM	randomized	5:2 vs CR	54 wks	↓7%	↓	↓	↓
ADF: Short term (<8 weeks)								
Soeters et al [33]	8 lean white men	randomized crossover	ADF vs standard diet	2 wks	Ø	Ø	Ø	-
Halberg et al [34]	8 lean men	single cohort	ADF	2 wks	Ø	Ø	Ø	-
Heilbronn et al [7]	16 lean men and women	single cohort	ADF men vs women	3 wks	↓3%	↓	↓	-
ADF: Moderate term (8-12 weeks)								
Klempel et al [9]	35 obese women	randomized	LF vs HF ADF	8 wks	↓5%	↓	Ø	↓ WC
Varady et al [43]	16 obese	single cohort	ADF	8 wks	↓6%	↓	Ø	-
Catenacci et al [36]	26 obese	randomized	ADF vs CR	8 wks	↓9%	↓	↓	↓**
Varady et al [10]	20 obese	single cohort	ADF	8 wks	↓6.5%	↓	Ø	-
Eshghinia et al [37]	15 women	single cohort	ADF	8 wks	↓7%	↓	-	↓ WC
Hoddy et al [8, 45]	74 obese men and women	randomized	ADF dinner vs lunch, vs small meals	8 wks	↓4%	↓	↓	↓
ADF: Long term (>12weeks)								
Varady et al [11]	32 normal weight and overweight	randomized control trial	ADF vs control	12 wks	↓7%	↓	Ø	-
Coutinho et al [38]	35 obese	randomized control trial	ADF vs CR vs control	12 wks	↓12.5%	↓	↓	-
Trepanowski et al [3]	100 obese	randomized control trial	ADF vs CR vs control	24 wks	↓7%	↓	Ø	↓

All changes reported are statistically significant within group (baseline to post-treatment). ** significant time x group interaction.
Ø no change
WC - waist circumference

Table 2: Effect of TRF on body weight and body composition

Reference	Subjects	Design	Intervention	Length (weeks)	Body weight	Fat mass	Fat-free mass	Visceral fat mass
TRF (<4h)								
Arnason et al [25]	10 T2DM	observational	4-6 h TRF	2 wks	↓1.5%	-	-	Ø WC
Tinsley et al [23]	28 lean resistance trained men	randomized	4d 4h TRF vs standard diet	8 wks	Ø	Ø	Ø	-
Stote et al [40]	21 normal weight	randomized crossover	1 meal (4h TRF) vs 3 meals/ day	8 wks	↓2%	↓	-	-
Carlson et al [39]	21 normal weight	randomized crossover	1 meal (4h TRF) vs 3 meals/ day	8 wks	↓2%	↓	-	-
TRF (>4 h)								
Teng et al [42]	56 men	RCT	5CR: 2 (2-d Ramadan fasting, 5-d CR)	12 wks	↓3%	↓	Ø	-
Kahleova et al [41]	54 T2DM	randomized crossover	2 meals (10h TRF) vs 6 meals/ day	12 wks	↓	-	-	↓**WC
Moro et al [22]	34 lean resistance trained men	randomized	8h TRF vs standard diet	8 wks	Ø	↓	Ø	-
Sutton et al [24]	8 pre-diabetic men	randomized crossover	6hr eTRF isocaloric and eucaloric	5 wks, 7 wk washout	Ø	-	-	-
Gill and Panda [21]	8 overweight	observational	10-12 h TRF	16 wks	↓4%	-	-	-

All changes reported are statistically significant within group (baseline to post-treatment).
** significant time x group interaction.
Ø no change
WC: Waist circumference

TRF

Although calories were set for weight maintenance, Stote et al [40] and Carlson et al [39] observed a significant decrease in body fat after 8 weeks of 4-h TRF (1 meal) versus 3 meals/day. Only two studies have examined the effect of >4-h TRF on fat mass [22, 42]. Teng et al [42] observed a significant decrease in fat mass after 5 days of CR combined with 2 days of Ramadan-style fasting for 12 weeks. Similarly, Moro et al [22] observed a significant decrease in body fat after 8 weeks of 8-h TRF.

2.2.2 Fat-free mass

5:2, 6:1 and ADF

Four studies have examined the effect of 6:1 or 5:2 on fat-free mass; and all resulted in decreased fat-free mass after 8-24 weeks [4-6, 31]. Three studies examined the effect of short-term ADF on fat-free mass [7, 33, 34]. No significant change was observed in fat-free mass after two 2-week ADF interventions [33, 34]. However, 3 weeks of ADF significantly decreased fat-free mass. As for the moderate-term ADF studies, Klempel et al [9] and Varady et al [10, 12] both observed no change in fat-free mass [9, 10, 12]. However, Catenacci et al [36] and Hoddy et al [8] observed a significant decrease in fat-free mass after 8 weeks of ADF intervention [8, 36]. Three long-term ADF studies have measured fat-free mass [3, 11, 38]. Varady et al [10] and Trepanowski et al [3] observed no change in fat-free mass after 12 weeks and 24 weeks of ADF interventions respectively. However, Coutinho et al [38] did observe a significant decrease in fat-free mass after 12 weeks of ADF. In traditional CR interventions, fat-free mass significantly decreases alongside changes in body fat. In summary, these studies suggest that fat-free mass generally decreases with 5:2, 6:1 and ADF.

TRF

Tinsley et al [23], Moro et al [22], and Teng et al [42] are the only TRF studies to measure fat-free mass. All three studies found no change in fat-free mass, however, Teng et al [42] is the only trial that resulted in significant weight loss [22, 23, 42]. It is also important to note that Tinsley et al [23] and Moro et al [22] did include resistance training in their interventions which may have been a confounding variable in their findings. Thus, the effect of TRF on fat-free mass remains inconclusive.

2.2.3 Visceral fat mass

6:1, 5:2 and ADF

Visceral fat mass is adipose tissue that lies under the peritoneum surrounding vital organs [1]. Elevations in visceral fat mass are highly corelated with an increase in insulin resistance leading to increased type 2 diabetes risk [1]. Increased visceral fat mass is also associated with dyslipidemia, hypertension and stroke, increasing the risk of cardiovascular disease [1]. Reductions in visceral fat mass and central obesity can improve both metabolic disease and cardiovascular disease risk-factors [1].

Nine studies have investigated the effect of 6:1, 5:2, and ADF on visceral-fat mass measured by dual x-ray absorptiometry (DXA), magnetic resonance imaging (MRI), or waist circumference [3, 4, 6, 8, 9, 12, 13, 31, 36, 37]. Kessler et al [31] did not observe significant change in visceral fat mass after 8 weeks of 6:1. Harvie et al [4] and Sundfør et al [13] both observed a significant decrease in waist circumference after 24 weeks of 5:2. Carter et al [5, 6] observed visceral fat mass significantly decrease after 24 weeks of the 5:2 diet. Four studies have examined the effect of moderate-term ADF on visceral fat mass or waist circumference [8, 9, 12, 36, 37]. Similar to 5:2, Klempel et al [9] and Eshghinia et al [37] both observed waist circumference decrease after 8 weeks of ADF. This remained significant regardless of if ADF consisted of a high-fat or low-fat diet [9]. Catenacci et al [36] did see significant decrease in trunk

fat after 8 weeks of ADF. When looking at fast day meal timing during ADF, Hoddy et al [8] observed a significant decrease overtime in waist circumference regardless if the fast day meal was consumed as a lunch, dinner or as small meals. Only one study has examined the long-term effects of ADF on visceral fat mass [3]. Trepanowski et al [3] observed visceral fat mass decrease significantly in the ADF group after 24 weeks. These data suggest that ADF may reduce visceral fat mass after 8 weeks of intervention. The effects of 6:1 or 5:2 on visceral fat mass are inconclusive and require additional research.

TRF

Two studies have measured waist circumference during TRF interventions [25, 41]. After 2 weeks of 4-6-h TRF, Arnason et al [25] did not see a significant change in waist circumference. However, Kahleova et al [41] did see a significant decrease in waist circumference when eating 2 meals/d versus 6 meals/d. Due to the limited evidence to date, the effects of TRF on visceral fat mass remain unclear.

3. Effect of intermittent fasting on metabolic disease risk factors

Changes in metabolic disease risk factors (plasma lipids, blood pressure, and glucoregulatory factors) during 6:1, 5:2 and ADF are displayed in **Table 3**. The effects of TRF on these variables are reported in **Table 4**.

3.1 LDL cholesterol

6:1, 5:2, and ADF

Low-density lipoproteins, or LDL cholesterol, are the main carriers of cholesterol in the circulation. Prolonged high LDL cholesterol levels increase lipid deposits in the arterial wall, hardening and narrowing the arteries. This hardening results in decreased blood flow leading to heart attacks, strokes,

and cardiovascular disease [1]. Research from both human and animal trials indicate that elevated low-density lipoprotein (LDL) levels (≥160 mg/dL) are a major cause of coronary heart disease (CHD) [46].

Four studies have examined the effect of 6:1 and 5:2 on LDL cholesterol [4, 6, 13, 32]. Zuo et al [32], Carter et al [6], and Harvie et al [4] observed significant reductions in LDL cholesterol (9-14%) after 5:2 intervention with 7-10% weight loss [4, 6, 32]. Sundfør et al [13] did not observe a significant change in LDL cholesterol after 24 weeks of 5:2, despite 8% weight loss [13]. ADF interventions less than 4 weeks did not affect LDL cholesterol levels [7, 33, 34]. After 8 weeks of ADF, Klempel et al [9], Varady et al [10], and Catenacci et al [36] all demonstrated significant decreases in LDL cholesterol (18-31%) with 5-7% weight loss, even in the presence of a high fat diet [9]. Conversely, Eshghinia et al [37] and Hoddy et al [8] did not observe any significant change in LDL cholesterol. Two studies have examined the effect of long-term ADF on LDL cholesterol [3, 11]. Varady et al [11] did not observe LDL cholesterol decrease after 32 weeks in normal and overweight subjects nor did Trepanowski et al [3] after 24 weeks of ADF in subjects with obesity, despite 7% weight loss in both groups. Overall, 5:2 and ADF may reduce circulating LDL cholesterol levels by 9-31 % after 8 weeks of intervention and with a minimum weight loss of >5%.

TRF

Six studies have examined the effect of TRF on LDL cholesterol [22, 24, 39-42]. In two studies involving a ≤4-h feeding window Stote et al [40] and Carlson et al [39] observed LDL cholesterol increase 20% after 8 weeks (1 meal a day group) [39, 40]. Four studies have examined the effect of >4-h TRF on LDL cholesterol [22, 24, 41, 42]. No significant change was observed in Sutton et al [24], Kahleova et al [41], or Moro et al [22] however, all these studies prescribed calories for weight maintenance. Conversely,

after 12 weeks of TRF, Teng et al [42] observed a significant decrease (8%) in LDL cholesterol with 3% weight loss. The effects of TRF on LDL cholesterol remain unclear and require additional investigation.

3.2 HDL cholesterol

6:1, 5:2, and ADF

Low HDL cholesterol is associated with increased cardiovascular disease risk, as it reflects a higher concentration of triglyceride rich lipoproteins [1]. HDL cholesterol mediates reverse cholesterol transport excreting the atherogenic plaque from the arteries improving endothelial function [47]. Increased HDL cholesterol may also increase glucose uptake into the skeletal muscle reducing blood glucose levels. It is currently thought that physical activity, not diet, might have the most positive impact on HDL cholesterol [48].

Five studies have examined the effect of the 6:1 or 5:2 on HDL cholesterol [4, 6, 13, 31, 32]. Zuo et al [32] and Carter et al [6] both observed HDL cholesterol significantly decrease (3-11%) after 5:2, with 7-10% weight loss. However, Kessler et al [31] and Harvie et al [4] observed no significant change in HDL cholesterol after 6:1 or 5:2 respectively. Sundfør et al [13] demonstrated an increase in HDL cholesterol (4%) after 24 weeks of 5:2 with 8% weight loss. As for short-term ADF, Heilbronn et al [7] observed a significant increase in HDL cholesterol (data not given) after 3 weeks of ADF, yet this change was only present in women. Five studies have monitored HDL in relation to moderate-term ADF [8-10, 36, 37]. While four of these studies [8-10, 37] observed no significant change in HDL cholesterol, Catenacci et al [36] demonstrated a significant decrease in HDL cholesterol (11%) after 8 weeks of ADF with 9% weight loss. In a longer-term study, Varady et al [11] did not observe a change in HDL cholesterol after 12 weeks despite a 7% weight loss. However, Trepanowski et al [3] observed HDL cholesterol significantly increase

(11%) after 24 weeks of ADF with 7% weight loss. Thus, 5:2 and ADF may lower HDL cholesterol levels in the short-term but raise HDL cholesterol levels after longer intervention periods (>24 weeks).

TRF

One study has examined ≤4-h TRF on HDL cholesterol [40]. In this study, Stote et al [40] observed a significant increase in HDL cholesterol (16 %) after 8 weeks of 4-h TRF (1 meal per day) versus 3 meals per day with 2% weight loss [40]. Four studies have examined the effect of >4-h TRF on HDL cholesterol [22, 24, 41, 42]. Sutton et al [24], Teng et al [42], and Kahelova et al [41] did not observe significant change in HDL cholesterol after TRF intervention. Moro et al [22] did, however, observe a significant increase in HDL cholesterol (7%) after 8 weeks of 8-h TRF in the absence of weight loss. Yet, Moro et al [22] examined TRF concurrently with resistance training which may have had an impact on this biomarker. Due to the paucity of data, the effect of TRF on HDL cholesterol levels is currently inconclusive.

3.3 Triglycerides

6:1, 5:2, ADF

Triglycerides play a key role in energy storage and dietary fat transport. Elevated triglycerides are a risk factor associated with metabolic disease as well as heart disease. While triglycerides tend to be elevated in populations with obesity, they are often ameliorated with a 5% decrease in body weight [2, 49]. Of the five studies that examined the effect of the 6:1 or 5:2 diet on triglycerides, four [4, 6, 13, 31, 32] found a significant reduction in triglycerides of 12-37% after weight loss of 5-10%. Kessler at al [31] did not observe a significant change in triglycerides after the 6:1 diet, however, this group also did not observe significant weight loss. In the short-term ADF studies, only Heilbronn et al [7] observed a significant decrease in triglycerides (data not shown) with 3% weight loss (male subjects only). In the

moderate-term ADF studies, Klempel et al [9], Varady et al [10, 12], and Catenacci et al [36] all demonstrated significant decreases in triglycerides (7-30%) after 8 weeks of ADF intervention and 4-9% weight loss. Conversely, Eshghinia et al [37] and Hoddy et al [8] observed no change in triglycerides, despite 4-7% weight loss. After long-term ADF, Varady et al [11] observed a significant decrease in triglycerides (20%) after 12 weeks of ADF with 7% weight loss as did Trepanowski et al [3] after 24 weeks (data not given) with 7% weight loss. Overall, it would appear as though the 5:2 diet and ADF produce relatively consistent decreases in triglycerides levels (7-37%) with 5-10% weight loss.

TRF

Two studies measured triglycerides in ≤4-h TRF, and both found no significant change after the intervention [39, 40]. As for the >4-h TRF studies, Teng et al [42] and Moro et al [22] observed no significant change in triglycerides after 8-12 weeks of intervention [22, 42]. However, one trial looking at 10-h TRF (2 meals/d) did see triglycerides decrease (data not given) significantly after 12 weeks [41]. Conversely, Sutton et al observed a significant increase in triglycerides (17%) after 5 weeks of 6-h TRF independent of weight loss. However, this change maybe due to increased lipolysis in response to the increased fasting time prior to measurement. Thus, it remains unclear if TRF has any beneficial impact on triglyceride levels.

Table 3: Effect of 6:1, 5:2, and ADF on metabolic disease risk factors

Reference	Subjects	Design	Intervention	Length (weeks)	TC	LDL	HDL	TG	BP	Glucoregulatory
6:1 diet										
Kessler et al [31]	36	non-randomized control	6: 1d fast vs control	8 wks	-	-	Ø	-	↓	Ø
Zuo et al [32]	40 overweight and obese	single cohort	6CR: 1 fast	12 wks	↓	↓	↓	↓	↓	-
5:2 diet										
Carter et al [5]	63 T2DM	randomized	5:2 vs CR	12 wks	-	-	-	-	-	↓HbA1c and medication effect score
Carter et al [6]	137 T2DM	randomized	5:2 vs CR	52 wks	↓	↓	↓	↓	-	↓HbA1c, fasting glucose, medication effect score
Sundfor et al [13]	112 obese	randomized	5:2 vs CR	24 wks	Ø	Ø	↑	↓	↓	↓HbA1c, no change in glucose
Harvie et al [4]	107 women	randomized	5:2 vs CR	24 wks	↓	↓	Ø	↓	↓	↓ Insulin and HOMA-IR
ADF: Short term (<8 weeks)										
Soeters et al [33]	8 lean white men	randomized crossover	ADF vs SD	2 wks	Ø	Ø	-	Ø	-	Ø
Halberg et al [34]	8 lean men	single cohort	ADF	2 wks	Ø	Ø	-	Ø	-	↑ Insulin mediated glucose uptake
Heilbronn et al [7]	16 lean men and women	single cohort	ADF men vs women	3 wks	Ø	Ø	↑	↓ Men	Ø	↓Insulin Post-prandial response M: Ø glucose, ↓Insulin W: ↓ glucose Ø Insulin
ADF: Moderate term (8-12 weeks)										
Klempel et al [9]	35 obese women	randomized	LF vs HF ADF	8 wks	↓	↓	Ø	↓	Ø	-
Varady et al [43]	16 obese subjects	single cohort	ADF	8 wks	↓	↓	Ø	↓	-	-
Catenacci et al [36]	26 obese subjects	randomized	ADF vs CR	8 wks	↓	↓	↓	↓	-	↓ Glucose
Varady et al [10]	20 obese subjects	single cohort	ADF	8 wks	↓	↓	Ø	↓	↓	-
Eshghinia et al [37]	15 women	single cohort	ADF	8 wks	Ø	Ø	Ø	Ø	Ø	Ø
Hoddy et al [8, 45]	74 obese men and women	randomized	ADF dinner vs Lunch, vs small meals	8 wks	Ø	Ø	Ø	Ø	↓ SM only	↓ Insulin in the most insulin resistant only

ADF: Long term (>12 weeks)										
Varady et al [11]	32 normal weight and obese	RCT	ADF vs control	12 wks	↓	↓	Ø	↓	-	-
Coutinho et al [38]	35 obese	RCT	ADF vs CR vs control	12 wks	-	-	-	-	-	↓Insulin
Trepanowski et al [3]	100 obese	RCT	ADF vs CR vs control	24 wks	Ø	Ø	↑	↓	Ø	↓Insulin and HOMA-IR

All changes reported are statistically significant within group (baseline to post-treatment).

** significant time x group interaction.

Ø no change.

Table 4: Effect of TRF on metabolic disease risk factors

Reference	Subjects	Design	Intervention	Length (weeks)	TC	LDL	HDL	TG	BP	Glucoregulatory
TRF (<4h)										
Arnason et al [25]	10 T2DM	observational	4-6 h TRF	2 wks	-	-	-	-	Ø	↓ post-prandial variability, ↑ glucose control, ↑subjects at AM glucose goal
Tinsley et al [23]	28 lean resistance trained men	randomized	4d 4-h TRF vs SD	8 wks	-	-	-	-	-	-
Stote et al [40]	21 normal weight	randomized crossover	1 meal (4h TRF) vs 3meals/ day	8 wks	↑	↑	↑	Ø	-	↓glucose control
Carlson et al [39]	21 normal weight	randomized crossover	1 meal (4h TRF) vs 3meals/ day	8 wks	↑	↑	-	Ø	-	↑ AM fasting plasma glucose
TRF (>4 h)										
Teng et al [42]	56 men	RCT	5CR: 2 Ramadan Fasting	12 wks	↓	↓	Ø	Ø	↓	Ø
Kahleova et al [41]	54 T2DM	randomized crossover	2 meals (10h TRF) vs 6 meals/ day	12 wks	Ø	Ø	Ø	↓	-	↓Glucose, Insulin and HbA1c
Moro et al [22]	34 lean resistance trained men	randomized	8h TRF vs SD	8 wks	Ø	Ø	↑	Ø	-	↓ Glucose, Insulin and HOMA-IR
Sutton et al [24]	8 pre-diabetic men	randomized crossover	6hr eTRF isocaloric and eucaloric	5 wks, 7 wk washout	↓	Ø	Ø	↑	↓	↓ fasting insulin ↓insulin levels at t = 60 min and 90 min post-load Improved B-cell function
Gill and Panda [21]	8 overweight	observational	10-12 h TRF	16 wks	-	-	-	-	-	-

All changes reported are statistically significant within group (baseline to post-treatment).
** significant time x group interaction.
Ø no change

3.4 Blood pressure

6:1, 5:2, ADF

Blood pressure is another common factor and diagnostic tool of both metabolic disease and heart disease risk. Blood pressure consists of the contraction phase (systolic blood pressure) and the relaxation phase (diastolic blood pressure) of the heart. When blood pressure is consistently high this increases the force, weakening arterial walls. This damage can lead to heart failure, renal disease, and peripheral vascular disease [1]. As with blood lipids, a weight loss of 5% can often normalize these measures [2].

All 6:1 and 5:2 studies examining the effect of these diets on blood pressure found significant decreases of 4-10mm Hg systolic and 4-8mm Hg diastolic with 5-10% weight loss [4, 13, 31, 32]. Only one study examined the effect of short-term ADF on blood pressure, however, no change was seen with 3% weight loss [7]. As for moderate-term ADF, Klempel et al [9] and Eshghinia et al [37] did not observe any improvement in blood pressure with 5-7% weight loss after 8 weeks of intervention. In contrast, Varady et al [10] did observe a significant improvement of 4.4 mm Hg systolic after 8 weeks of ADF and 6% weight loss . Hoddy et al [8] reported a significant decrease in blood pressure (6 mm Hg, systolic) after 8 weeks of ADF and 4% weight loss. However, this improvement was only seen in the meal timing group which had the highest blood pressure at baseline [8]. In one long-term study of ADF, Trepanowski et al [3] reported no change in blood pressure in normotensive obese adults, despite 7% weight loss. At present, it is unclear if 6:1, 5:2, or ADF affect blood pressure as all previous trials have implemented healthy normo-tensive subjects. The effects of these diets on individuals with elevated blood pressure at baseline is of great interest.

TRF

Only three studies have examined the effect of TRF on blood pressure [24, 25, 42]. Arnason et al did not observe any change in blood pressure after two weeks of 4-6-h TRF [25]. However, after 12 weeks of a TRF diet, Teng et al did observe significant blood pressure reductions of 7 mm Hg systolic and 2 mm Hg diastolic. Sutton et al [24] also observed a significant decrease in blood pressure (11mm Hg systolic and 10 mm HG diastolic) after 5 weeks of 6-h TRF independent of weight loss. There is not enough data currently to determine the effect of TRF on blood pressure, however, it may be possible that TRF longer than two weeks may improve blood pressure, even in normotensive individuals.

3.5 Glucose

6:1, 5:2, and ADF

Elevated blood glucose is one of the main factors utilized in the diagnosis of metabolic disease. Consistently high blood glucose can lead to damage of blood vessels resulting in increased heart disease risk as well as insulin resistance [1, 50]. Diet, exercise, and weight loss have been shown to positively impact glucose regulation [50]. Three studies have examined the effect of 6:1 or 5:2 on blood glucose [4, 6, 13]. Carter et al [6] is the only group to observe a decrease in fasting glucose (12%) after 52 weeks of 5:2 with 7% weight loss [4, 6, 13]. It is also important to note Carter et al [5, 6] did encourage an increase in steps/day with the 5:2 intervention which could improve glucose uptake by skeletal muscle [51]. Eight studies have examined the effect of ADF on blood-glucose levels [3, 7, 8, 33-38, 45]. Three studies measured glucose after short-term ADF [7, 33-35]. While Soeters et al [33] did not demonstrate a significant change in glucose after 2 weeks of ADF, Halberg et al [34] observed a significant increase in insulin mediated glucose uptake. Heilbronn et al [7] also observed post-prandial

glucose decrease (data not shown) in women after only 3 weeks of ADF [7]. Three moderate-term studies examined the effect of 8 weeks of ADF on glucose [36, 37, 45], however Catenacci et al [36] is the only group to demonstrate significant increase in glucose (7%) with 9% weight loss. Two long-term studies have measured glucose; neither observed a significant change after intervention [3, 38]. Thus, it does not appear that 5:2 or ADF have a significant effect on fasting glucose levels.

TRF

Seven studies have examined the effect of TRF on glucose [22, 24, 25, 39-42]. In subjects with Type 2 diabetes post-prandial variability decreased, glucose control increased, and the number of subjects at their morning glucose goal increased after 2 weeks of 4-h TRF [25]. Conversely, after 8 weeks of 1 meal/day (4-h feeding window) Stote et al [40] and Carlson et al [39] observed normal weight subjects decrease their glucose control and increase their morning fasting plasma glucose (7%) [39, 40]. Four studies have examined the effect of >4-h TRF on glucose [22, 24, 41, 42]. Sutton et al [24] and Teng et al [42] did not observe significant change post intervention. However, Kahleova et al [41] and Moro et al [22] did demonstrate a significant decrease in glucose (data not shown for Kahelova et al, 11% in Moro et al) after 10-h and 8-h TRF respectively in the absence of weight loss. While these preliminary data are promising, it is currently unclear if TRF has any impact on glucose levels.

3.6 Insulin

6:1, 5:2, and ADF

As plasma glucose levels rise, beta-cells in the pancreas increase their insulin output to dispose of the increased glucose load. But, consistently high insulin levels can progress to insulin resistance and

decreased functioning of beta-cells leading to metabolic disease and increased risk of heart disease [1]. Nine studies have examined the effect of 6:1, 5:2, or ADF on fasting insulin [3, 4, 7, 31, 33-38, 45]. Kessler et al [31] did not observe any change in fasting insulin after 8 weeks of 6:1. However, Harvie et al [4] did demonstrate a significant decrease in insulin (29%) after 24 weeks of the 5:2 diet [4]. Three trials have examined short-term ADF and its effect on fasting insulin [7, 33-35]. While Soeters et al [33] did not demonstrate a significant change in insulin after 2 weeks of ADF, Halberg et al [34] observed an increase in insulin-mediated glucose uptake. Heilbronn et al [7] also observed a significant decrease in fasting insulin (data not shown) in both men and women and a decrease in post-prandial insulin in men [35]. Three studies measured fasting insulin after moderate-term ADF [36, 37, 45]. Catenacci et al [36] and Eshghinia et al [37] both observed no change in insulin post intervention. However, after Hoddy et al [45] stratified subjects by baseline insulin resistance (utilizing hemostatic model assessment of insulin resistance), this group found that those that were the most insulin resistant at baseline had the largest decrease in insulin post ADF intervention [8, 45]. This improvement in insulin resistant subjects was maintained regardless of when they ate their fasting meal [8, 45]. Two studies have measured the impact of long-term ADF on fasting insulin levels [3, 38]. Both Coutinho et al [38] and Trepanowski et al [3] observed a significant decrease in insulin after 12 weeks (data not shown for Coutinho et al) and 24 weeks of ADF (47%) respectively. It appears that 6:1, 5:2, and ADF may be effective diet therapies to lower fasting insulin levels, especially in those that are insulin resistant at baseline.

TRF

Only four studies have examined the effect of TRF on insulin (Table 4) [22, 24, 41, 42]. Sutton et al [24] demonstrated a significant decrease in fasting insulin (14%) as well as a significant decrease in insulin

at 60 and 90 min post caloric load independent of weight loss. Despite eating calories for weight maintenance, Kahelova et al [41] and Moro et al [22] both observed a significant decrease in insulin after 10-h and 8-h TRF respectively. Teng et al [42] did not observe a change in insulin after 12 weeks of 5:2 CR:TRF. While the research remains inconclusive regarding the effect of TRF on insulin, current data are promising.

3.7 Insulin resistance and HbA1c

Insulin resistance is a main contributing factor to increasing risk of both metabolic disease and cardiovascular disease. Insulin resistance occurs after long periods of high blood glucose. Insulin release is increased by the beta-cells of the pancreas in order to dispose of excess glucose. Over time this influx of insulin will cause skeletal and peripheral muscle cells to be unable to utilize insulin correctly, leading to type 2 diabetes. Changes in diet, exercise, and weight loss have all been found to improve insulin resistance [50]. The homeostasis model assessment of insulin resistance (HOMA-IR) has been shown to be a reliable index to predict insulin resistance [52, 53]. The HOMA-IR equation predicts insulin response by utilizing a ratio of fasting insulin to fasting glucose [HOMA-IR = Fasting insulin (μlU/ml) × Fasting glucose (mg/dL) / 405]. In contrast, hemoglobin A1C (HbA1c) is the measure of average daily blood glucose over the past 2-3 months by measuring glycosylated hemoglobin (i.e. glucose attached to red blood cells). HbA1c can point to effectiveness of insulin over the last 3 months as this is the lifespan of a red blood cell. Each 1% change in HbA1c correlates with a 35 mg/dL change in average daily blood glucose [1].

6:1, 5:2, and ADF

Three studies have examined the effect of 6:1, 5:2, or ADF on insulin resistance and HbA1c [3, 5, 6]. Two studies from the Carter et al [5, 6] group examined insulin resistance after 12 weeks and 52 weeks of 5:2 versus CR in subjects with type two diabetes mellitus (T2DM). Both studies observed a significant decrease in HbA1c (-0.3%) after the intervention with 6-7% weight loss, suggesting improved glycemic control [5, 6]. Trepanowski et al [3] is the only ADF study to examine the effect of the diet on insulin resistance. This study reported a significant decrease in HOMA-IR (-2.5) after 24 weeks of ADF with 7% weight loss. These preliminary data offer promise for the use of fasting interventions in decreasing HbA1c levels.

TRF

Three studies have examined the effect of TRF on insulin resistance and HbA1c [22, 25, 41]. Arnason et al [25] found no significant change in HOMA-IR after 2 weeks of 4-h TRF [25]. Two studies examined the effect of >4-h TRF on insulin resistance [22, 41]. Kahleova et al [41] observed HbA1c significantly decrease (-1.8) after 2 meals/day in subjects with T2DM. Moro et al [22] observed HOMA-IR decrease (-43%) with 8-h TRF after 8 weeks. It is possible that insulin resistance may be improved after TRF lasting longer than 2 weeks. However, more studies are needed to confirm these findings.

4. Safety

Although intermittent fasting appears to have beneficial effects on body weight and some metabolic disease risk factors, the safety of these diets has been questioned. The effects of caloric restriction and

intermittent fasting on key safety indicators (complete blood count, adverse events, eating disorder symptoms, body image perception, and eating behaviors) are reviewed below.

4.1 Resting metabolic rate (RMR)

6:1, 5:2, ADF

Dieting and weight loss are often associated with a decline in resting metabolic rate. This decrease in resting metabolic rate with weight loss may make maintenance more difficult as subjects need to continually eat less in order to maintain caloric restriction. A decrease in resting metabolic rate also generally indicates loss of lean mass [54]. One study has evaluated the effect of 5:2 on resting metabolic rate [13]. In this study [13], resting metabolic rate was reduced by 100 kcal/day, in response to 8% weight loss. Three studies have evaluated the effect of ADF on resting metabolic rate [7, 36, 38]. Heilbronn et al [7] did not observe significant change in resting metabolic rate after 3 weeks of short-term ADF in normal-weight subjects [7]. Catenacci et al [36] observed a significant decrease in resting metabolic rate (-101 Kcal/d) after 8 weeks of moderate-term ADF and 9% weight loss. This study [36] also examined a daily CR group. When resting metabolic rate was adjusted for fat mass and fat-free mass, only the CR group had a significant decrease in resting metabolic rate (-111 Kcal/d), no between group differences were reported [36]. Coutinho et al [38] resulted in a significant decrease in resting metabolic rate in the ADF (-120 Kcal/d) group after long-term intervention, however no difference between the ADF and CR group was observed. It appears that the 5:2 diet and ADF result in mild reductions in resting metabolic rate with weight loss (-100-200 kcal/d), but these reductions are similar to what is seen with daily calorie restriction regimens.

TRF

Two studies have examined the effect of TRF on resting metabolic rate [22, 41]. Moro et al [22] did not observe a significant change in resting metabolic rate after 8 weeks of 8-h TRF, however, subjects were eating for weight maintenance and physically active during the intervention which may ameliorate this effect. Kahelova et al [41] determined resting energy expenditure through indirect calorimetry and reported a significant decrease in both the 2 meal/day (-91 Kcal/d) and 6 meal/day (-108 Kcal/d) groups after the 12-week intervention, however there were no between group differences. The effect of TRF on resting metabolic rate remains unclear as data are limited.

4.2 Complete blood count

A complete blood count (CBC) is a widely used blood test to evaluate overall health. One study has examined the effect of a caloric resctrition on CBC [55]. In this study, Basciani et al [55] did not see any significant change in CBC after 30 days of a very-low-calorie diet (VLCD) (700kcal/d) or after 30 days of a low-calorie diet (LCD) (1100kcal/d). One study has evaluated the effect of TRF on CBC [40]. In this study, reducing meal frequency to one 4-h window daily, Stote et al demonstrated that complete blood count did not change in normal-weight adult subjects. These preliminary findings suggest that these regimens may be well tolerated by normal weight and adults with obesity, however more data are evidently needed.

4.3 Adverse events

Adverse events are generally monitored during clinical trials in order to evaluate the safety of the dietary intervention for the general population. Furthermore, adverse events can decrease both

adherence and efficacy of a diet. Increased frequency of constipation, irritability and fatigue are common safety concerns with all forms intermittent fasting [26]. One study has examined adverse events during a 5:2 intervention [13]. In a study by Sundfor et al [13], no serious adverse events were reported during a 24-week intervention, and most minor adverse events in both the CR and 5:2 diet groups were reported in the first 4 weeks of trial. One study has examined adverse events in ADF [26]. 8-weeks ADF did not increase the frequency of gastrointestinal events (constipation, diarrhea, water retention or bad breath) in adults with obesity [26]. Rates of dizziness, general weakness, or sleep disturbances also did not increase with moderate-term ADF [26]. Hoddy et al [26] demonstrated that the rate of adverse events reported with ADF appears to be like that of daily CR. Sutton et al [24] is the only study to report adverse events possibly related to 6-h TRF including vomiting, frequent urination, drowsiness, headaches, increased thirst and diarrhea. No serious adverse events were reported throughout the intervention [24]. These results suggest that ADF and TRF are generally well tolerated with no serious adverse events, however more data are needed to assert this claim.

4.4 Eating disorder symptoms

It has been speculated that fasting or dietary restriction may increase eating disorder symptoms [56-58]. Eating disorder symptoms are often assessed using the multi-dimensional assessment of eating disorder symptoms (MEADS)[59]. The MEADS self-report breaks down eating disorder symptoms into six domains: binge eating, restrictive eating, purgative behavior, fear of fatness, avoidance of forbidden foods and depression. Recent data suggest however, that fasting and consistent dietary restriction may not effect eating disorder symptoms as speculated. For instance, in a recent study by Williamson et al [60], it was demonstrated that 25% daily restriction did not increase eating disorder symptoms and had

no other harmful psychological effects. Likewise, 8 weeks of ADF has been shown to have no negative impact on eating disorder symptoms in adults with obesity, specifically no change was seen in purgative behavior, fear of fatness and avoidance of forbidden foods [26]. Indeed, ADF may have beneficial effects by increasing dietary restraint [26, 61]. Hoddy et al [26] observed restrictive eating increase, suggesting that the ADF intervention may have helped control unrestrained eating behaviors. This group also observed decreased depression scores decrease after 8 weeks of ADF [26]. CR and ADF do not appear to increase eating disorder symptoms, however, more research should be done in order to confirm this finding.

Most eating disorders in subjects with overweight and obesity involve binge eating [62]. Binge eating disorder (BED) is categorized by eating large amounts of food with a feeling of loss of control. Diagnosis is usually dependent on binge eating episodes that occur at least once a week for 3 months [63, 64]. It has been speculated that intermittent fasting or CR may increase incidence of binge eating episodes in this population [62]. Wadden et al [65] examined the effect of CR or CR in combination with meal replacements, versus a control group on binge eating disorders. After the first 9 weeks, which was the most restrictive phase, no binge eating episodes were reported in any group. At week 20, two binge eating episodes were reported in the CR group and none in the CR with meal replacement. At week 28 there was a significant difference between groups in which 4 participants in the CR with meal replacement group were judged to have had one objective binge episode and a fifth woman had 2 episodes. No episodes were observed in the two other groups at 28 weeks. There was no differences between groups in subjective binge eating episodes [65]. In a review on the effect of CR on binge eating, no consistent association was seen between caloric restriction and the occurrence of binge

eating episodes in those previously undiagnosed with binge eating disorder. This review speculated that severe energy restriction may have beneficial effects with subclinical binge eating [63]. The national task force on the prevention and treatment of obesity also did a review of the effect of CR on binge eating and found that weight loss interventions do not seem to cause clinically significant binge eating in those without pre-existing episodes and may ameliorate binge eating prior to receiving treatment for the disorder. Weight loss interventions may improve psychological status however, this may return to baseline with weight regain [62]. Only one study has examined binge eating disorder symptoms and ADF [26]. Hoddy et al [26] observed binge eating symptoms decrease after 8 weeks of ADF. CR and ADF do not seem to increase episodes of binge eating, however more data are needed to make this conclusion.

4.5 Body image perception

The body shape questionnaire (BSQ) is a validated questionnaire that measures excessive concern about one's body size and shape [66]. Negative perception and attitudes about the body's appearance have been considered to be a main qualifier of anorexia nervosa and bulimia [66]. Higher scores on the BSQ indicate greater concerns with body size and shape [66]. After CR and CR in combination with meal replacement, Wadden et al [65] observed large reductions in negative body image. Similarly, Hoddy et al [26] observed a significant decrease in concern about body size and shape after 8 weeks of ADF. More data are needed but, weight loss interventions may improve body-image perception.

4.6 Eating behaviors

The three-factor eating questionnaire (TFEQ) assesses eating behavior in three domains utilizing a self-report questionnaire. These three domains are cognitive restraint, emotional eating, and uncontrolled eating [67]. In the TFEQ, cognitive restraint considers the subject's ability of both cognitive and behavioral strategies to reduce intake. Emotional eating and uncontrolled eating measure compulsive food intake when a subject may feel out of control. Higher scores of emotional eating and uncontrolled eating often point to overeating and binge eating [68]. An increase in cognitive restraint and a decrease in emotional and uncontrolled eating can have a positive effect on subjects after caloric restriction or fasting. Chaput et al [69] observed a significant increase in dietary restraint and decrease in disinhibition and susceptibility to hunger after both 5kg and 10kg of body-weight loss. Keranen et al [70] found that both the standard diet-education group and an intensive diet-education intervention group increased dietary restraint significantly after 72 weeks. Those who increased their cognitive restraint were more successful in maintaining their weight loss and the more cognitive restraint increased, the more the energy intake decreased. However, changes in uncontrolled and emotional eating did not correlate with a change in dietary intake [70]. More data are needed evaluate the effect of CR and intermittent fasting on eating behaviors, however it is possible that changes in these eating behaviors may help with weight maintenance rather than increase eating disorder symptoms.

5. Sleep and caloric restriction

5.1 Weight loss and sleep

Only 35% of adults meet the recommended 7-9-h of sleep each night [71]. Obesity is associated with poor sleep quality and shorter sleep duration [27-29]. A recent review observed a consistent

association between short sleep and higher total energy and fat intake, as well as lower fruit intake and lower overall quality of diet [72]. Conversely, weight loss by means of dietary restriction may help improve sleep quality and quantity [73, 74]. The Pittsburgh Sleep Quality Index (PSQI) is often used to measure sleep quality, timing, and duration. This 19-item self-report survey measures total sleep quality in the past month, yielding a total score of 0-21. 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 [75]. Chauput et al [69] evaluated weight loss in 11 men with obesity, they reported significantly improved sleep quality after 5 kg of weight loss. The CALERIE study [74] also reported a significant improvement in subjective sleep quality, sleep duration, overall PSQI scores at week 52 after 12% weight loss, no between group differences were found. These changes did not remain significant at follow-up at 104 weeks [74]. The POWER-UP study [73] also evaluated the effect of weight loss on sleep quality and duration. This group evaluated the effect of usual care, brief lifestyle counseling, or enhanced lifestyle counseling with a healthy diet and physical activity prescription. At 24 weeks the mean minutes of sleep increased significantly in the group who lost ≥5% body weight. At 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 over time at 104 weeks; no between group differences were seen. PSQI scores also improved significantly in those that lost ≥5% at 24 weeks however, at 104 weeks this was no longer significant [73]. Verhoef et al [76] reported significant improvements in daytime sleepiness and time to fall asleep during the 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 [76]. 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.

5.2 Fasting and sleep

Evidence from animal studies suggests that TRF lowers body weight in a way that may improve circadian rhythmicity and sleep [77]. However, data on the effect of fasting on sleep quality and duration are limited. Currently, only two studies have evaluated the effect of fasting on sleep or circadian patterns [21, 78]. 10-h TRF resulted in 4% weight loss and improved self-reported sleep in participants with overweight over 16 weeks [21]. Almeneessier et al [78] 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. More data are needed to determine the effect of fasting on sleep quality, quantity, and circadian patterns.

5.3 Meal timing and sleep

Data regarding the effect of meal timing on sleep are limited. However, it has been speculated that sleep duration may influence timing of food intake or vice versa [79]. After evaluating NHANES data from 2005-2010, Kant and Grabard [79] revealed an association between short-duration sleepers reporting the earliest onset of eating and latest conclusion of eating. Also, these short sleepers reported eating a higher calorie intake during snacking than at main meals [79]. Garaulet et al [80] reported that earlier meal timing may increase effectiveness of a Mediterranean diet weight-loss intervention, however, no effect was seen on sleep duration between early and late eaters. The effect of meal timing on sleep quality and duration is unclear; more data are needed to determine this effect.

6. Impact of energy free beverage intake while fasting on appetite control

Fasting regimens (6:1, 5:2, ADF, and TRF) all include water fasting as a component of the intervention. Often calorie free drinks such as diet soda, black tea, and black coffee are allowed during the water fasting window to help blunt hunger. However, it is speculated that sugar-free sweeteners and caffeine may affect appetite regulation [81-93].

6.1 Effect of sugar-free beverages on appetite control

Non-calorie sweeteners have been utilized as a tool for weight management by adding sweetness to products without adding to the caloric density. While some have found this substitution may facilitate weight loss, most of these data are epidemiological rather than prospective [90, 91]. Other studies have suggested that those with overweight and obesity might be more likely to use these products and that long-term use of low-calorie sweeteners may lead to weight gain [90, 91]. The mechanism speculated to increase weight via non-calorie sweeteners is thought to be linked between psycho-physiological pathways [91]. It is thought that the de-coupling of the body's response to sweet taste and the lack of caloric load of the non-calorie sweetened food may disturb the body's natural food-regulation system and increase appetite [90]. A study from Holt et al [93] examined the relationship between sugar-free versus sugar-rich beverages on feelings of fullness and subsequent food intake. Sugar-free soft drinks had significantly lower ratings for hunger after 50 minutes than mineral water and significantly lower ratings for fullness at 40 minutes. No significant difference in caloric intake after beverage consumption were seen except for the 35-50-minute time period, when significantly fewer chips were consumed by the mineral water drink than the sugar-free drink [93]. Steinert et al [92] examined the effect of sugars and artificial sweeteners on appetite and secretion of satiety peptides

utilizing a nasogastric feeding tube bypassing the taste receptors on the tongue. This group observed that gut hormone secretion of GLP-1, PYY and ghrelin was only affected by glucose, and to a small extent fructose. Sugar substitutes did not have a significant effect on gut hormone secretion. Hunger and fullness were not significantly different from water in any treatment group [92]. A study from Hill et al [90] examined the role of non-caloric sweeteners on cognition, food choice, and post-consumption satisfaction. They reported a significant increase in recognition of high-fat foods in the non-calorie sweetened beverage group versus the sugar-sweetened beverage or mineral water group. The non-calorie sweetener group was almost 3 times more likely to consume candy than the sugar-sweetened or mineral water groups. The non-calorie sweetened group was also less satisfied after cookie consumption than the sugar-sweetened or mineral water groups [90]. Effect of non-calorie sweetened beverages on weight and appetite continues to be divided. However, the de-coupling of sweet taste and caloric intake may increase desire to eat higher calorie-dense foods and decrease satisfaction with these higher calorie foods after consumption. Over the long term this may increase calorie intake and cause subjects who drink non-calorie sweetened beverages to make poorer choices during the intermittent fasting feeding window, however studies should be done to directly examine this effect.

6.2 Effect of caffeine on appetite control

According to epidemiological evidence there is a negative association between coffee/caffeine consumption and bodyweight gain long-term [82, 87]. However, current studies are still examining if this correlation is due to increased energy expenditure, decreased intake, or decreased appetite [81-89, 94]. Hursel et al [85] examined the relationship of catechin-rich teas (green tea and oolong tea) and

caffeine on energy expenditure and fat oxidation. This meta-analysis observed a dose-dependent significant increase in energy expenditure in the catechin-rich tea and caffeine groups. However, fat oxidation only increased in the catechin-rich tea group and not the caffeine group when compared to the placebo [85]. A double-blind randomized control trial recently examined the effect of caffeine on energy expenditure [86]. Júdice et al [86] observed no changes in totally energy expenditure or physical activity, however caffeine had significantly less total sleep time than the placebo group. Gaverieli et al [83] examined the effect of coffee and decaffeinated coffee on energy intake, appetite and inflammation in healthy men. This group did not observe an effect of caffeine on hunger, satiety, or desire to eat, energy intake or hunger hormones. However, at 180 min after ingestion, the caffeine group reported a significantly lower desire to eat than the decaf group. Serum cortisol levels remained higher in the caffeine group than both the decaf and control group except at 90 minutes. At this time-point all three groups were significantly different from each other with cortisol being the highest in the caffeine group and lowest in the control group. Glucose concentrations were also higher at 60 minutes in the caffeine group than the control group [83]. This same group [82] then examined the effect of different amounts of coffee on dietary intake and appetite in normal-weight versus participants with overweight and obesity. They observed that increased coffee intake in the group with overweight and obesity reduced energy intake during the ad libitum meal following beverage consumption compared to the moderate-coffee group. Total daily calorie intake was significantly less in the high coffee group than the moderate coffee group or the water group. Appetite feelings did not differ in any group [82]. This suggests that higher coffee intake may lead to decreased energy intake. However, in a double-blind randomized control trial, Schubert et al [89] did not find any difference between water, decaffeinated coffee, caffeine, and caffeine with decaffeinated coffee in energy intake, gastric

emptying, appetite sensations or plasma glucose. Data are split on whether caffeine may increase energy expenditure or reduce energy intake; further studies should be done to determine this effect.

It is important to note that multiple studies have investigated the effect of caffeine intake on glucose, insulin, and insulin resistance [84, 88, 89, 94]. MacKenzie et al [88] observed a significant improvement in HOMA-IR yet no significant difference in insulin or glucose. However, Graham et al [84] and Robinson et al [94] found that caffeine intake increased and prolonged plasma insulin and glucose in the meal following caffeine ingestion. These data suggest that caffeine could lead to increased insulin resistance, and could have a negative effect on weight gain or metabolic disease risk longer-term. It is unclear the true effect of caffeine intake on appetite or energy intake and expenditure. Whether or not fasting regimens should allow caffeine intake during the fasting window is still unclear.

III. MANUSCRIPT 1

Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study (Published in Nutrition and Healthy Aging, 4, 2018, 345-353)

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Running head: Time restricted feeding effect on body weight

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1. Abstract

Background: Time restricted feeding decreases energy intake without calorie counting and may be a viable option for weight loss. However, the effect of this diet on body weight in obese subjects has never been examined. **Objective:** This study investigated the effects of 8-h time restricted feeding on body weight and metabolic disease risk factors in obese adults. **Design:** Obese subjects (n = 23) participated in an 8-h time restricted feeding intervention (ad libitum feeding between 10:00 to 18:00 h, water fasting between 18:00 to 10:00 h) for 12 weeks. Weight loss and other outcomes were compared to a matched historical control group (n = 23). **Results:** Body weight and energy intake decreased in the time restricted group (-2.6% ± 0.5; -341 ± 53 kcal/d) relative to controls over 12 weeks ($P < 0.05$). Systolic blood pressure decreased in the time restricted feeding group (-7 ± 2 mm Hg) versus controls ($P < 0.05$). Fat mass, lean mass, visceral fat mass, diastolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, HOMA-IR, and homocysteine were not significantly different form the control group after 12 weeks (no group × time interaction). **Conclusions:** These findings suggest that 8-h time restricted feeding produces mild caloric restriction and weight loss, without calorie counting. It may also offer clinical benefits by reducing blood pressure.

Key words: Time restricted feeding, intermittent fasting, body weight, metabolic disease risk factors, obese adults

2. Introduction

Intermittent fasting has gained considerable popularity over the past decade. There are two major subcategories of intermittent fasting: 1) fasting 1-4 d per week, i.e. alternate day fasting or the 5:2 diet [95]; or 2) fasting every day for a 14 to 20 h period, i.e. time restricted feeding [15, 96]. Alternate day fasting and 5:2 are the most widely studied forms of intermittent fasting [4, 7-9, 36, 97, 98]. Human trials of alternate day fasting and 5:2 generally demonstrate reductions in body weight of 3 to 8% after 8 to 52 weeks of treatment, accompanied by decreases in blood pressure, LDL cholesterol, triglycerides, and insulin resistance [4, 7-9, 36, 97, 98]. The effects of time restricted feeding on the other hand, have only been tested in three human trials to date [21, 22, 99]. Gill and Panda [21] examined the effects of 10-h time restricted feeding in overweight healthy adults and showed a 4% weight loss that was sustained for one year. Findings from the other two studies [22, 99] reveal that 4-8 h time restricted feeding reduces caloric intake (without calorie counting) and significantly decreases fat mass without changing lean mass in young resistance trained men. While these preliminary studies offer promise for the use of time restricted feeding in reducing energy intake and fat mass, additional trials are necessary confirm these findings.

Obesity greatly increases the risk of metabolic diseases, such a coronary heart disease and type 2 diabetes [100]. Accumulating evidence suggests that even small amounts of weight loss can lead to improvements in metabolic health [101]. Although alternate day fasting and 5:2 have been shown to be effective for weight loss [4, 7-9, 36, 97], recent research suggests that obese individuals may have difficulties sticking to these diets long-term [98]. Time restricted feeding is an attractive alternative to alternate day fasting and 5:2, as this diet allows for ad libitum feeding within a large window of time

each day, and does not require any calorie counting [15, 96]. However, no trial to date has examined whether time restricted feeding is indeed an effective diet therapy for weight loss in obese subjects.

Accordingly, this study compared the effects of an 8-h time restricted feeding regimen versus a no-intervention historical control group on body weight and metabolic disease risk factors in obese adults. We hypothesized that the time restricted feeding group would lose weight and improve blood pressure, plasma lipids, and glucoregulatory factors versus control subjects after 12 weeks of treatment.

3. Methods

Time restricted feeding subject selection

A 12-week trial was implemented to test the effects of time restricted feeding versus matched historical controls on body weight and metabolic disease risk factors. 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. Time restricted feeding subjects were recruited from September 2016 to January 2017 from the Chicago area via advertisements placed around the University of Illinois Chicago campus. A total of 40 subjects were consented and assessed for eligibility to participate in the time restricted feeding intervention (**Figure 1**). Of these 40 subjects, 11 subjects were excluded because they did not meet one or more inclusion criteria, and 6 subjects declined to participate after qualifying. Inclusion criteria was as follows: BMI between 30 and 45 kg/m^2; age between 25 and 65 years; pre-menopausal or post-menopausal

(absence of menses for more than 2 years); sedentary to lightly active (<7500 steps/d); weight stable for 3 months prior to the beginning of the study (< 4 kg weight loss or weight gain); non-diabetic; no history of cardiovascular disease (myocardial infarction or stroke); non-smoker; not a shift worker; and not taking weight loss, lipid- or glucose-lowering medications.

Historical control subject selection

Outcome measures were compared to a matched historical control group from a previous weight loss trial performed by our group from October 2011 to January 2015 [98] (**Figure 1**). This previous trial implemented similar inclusion and exclusion criteria as the present trial, and all control subjects were recruited from the Chicago area via advertisements placed around the University of Illinois Chicago campus. There were 31 control subjects in the pervious trial [98]. A stratified random sampling protocol based on age, BMI, and sex was used to match the historical control group (n = 23) to that of the time restricted feeding group (n = 23). Subjects were randomly selected from each consecutive strata, one-by one, until the sample size of 23 was reached.

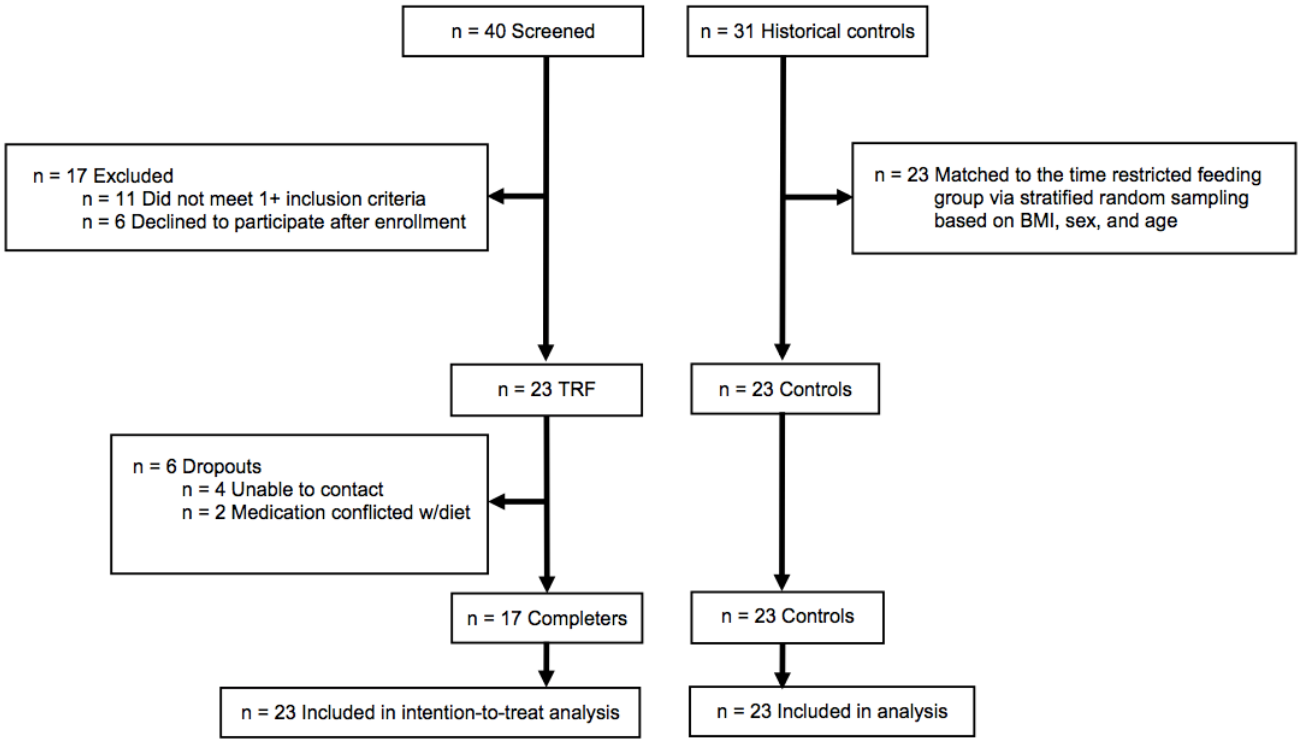

Figure 1 - Study Flow Chart

Time restricted feeding group protocol

Time restricted feeding subjects were instructed to eat ad libitum from 10:00 to 18:00 h daily, and fast from 18:00 to 10:00 h daily. During the 8-h feeding window, there were no restrictions on types or quantities of foods consumed. Moreover, subjects were not required to monitor caloric intake during ad libitum feeding period. During the fasting period, subjects were encouraged to drink plenty of water and were permitted to consume energy-free beverages, such black tea, coffee, and diet sodas. Adherence to the 8-h time restricted feeding window 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 8-h window (10:00 to 18:00 h), that day was labeled “adherent”. If the log indicated that the subject consumed food outside of the 8-h feeding window, that day was labeled as

"non-adherent". Adherence to the time restricted feeding diet was assessed as the number of adherent days per week.

Historical control group protocol

Historical controls were instructed to maintain their weight throughout the trial, and not to change their eating or physical activity habits. During a previous weight loss trail performed by our group from 2011-2015 (10) control subjects visited the research center on a weekly basis for weigh-ins. Body composition and metabolic disease risk variables were assessed in control subjects every 12 weeks.

Dietary intake and physical activity

Time restricted feeding and control subjects completed a 7-d food record at baseline (prior to commencing the study) and week 12. At baseline, 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. The timing of food intake was also recorded. Subjects 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). Food records were collected at the weigh-in at baseline and week 12, 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, fat, protein, carbohydrate, cholesterol, and fiber. All subjects were asked to maintain

their level of physical activity throughout the entire trial. We assessed activity level by steps/d. Step counts were measured over 7-d at baseline (prior to commencing the study) and week 12 by a pedometer (Yamax Digi-walker SW-200, Yamax Inc., San Antonio, TX).

Outcome measures

Body weight and body composition

The primary outcome measure was body weight. Body weight was assessed to the nearest 0.25 kg at the beginning of every week without shoes and in light clothing using a balance beam scale (HealthOMeter, Boca Raton, FL). Height was assessed at time recruitment and at baseline week 1 using a wall-mounted stadiometer to the nearest 0.1 cm. BMI was assessed as kg/m^2. Body composition (fat mass, lean mass, visceral fat mass) was measured using dual x-ray absorptiometry (DXA; iDXA, General Electric Inc).

Metabolic disease risk factors

Blood pressure and heart rate were measured at baseline and week 12 in triplicate using a digital automatic blood pressure/heart rate monitor (Omron HEM 705 LP, Kyoto, Japan) with the subject in a seated position after a 10-min rest. Twelve-h fasting blood samples were collected between 5:00 and 9:00 h at baseline and week 12. The subjects were instructed to avoid exercise, alcohol, and coffee for 24 h before each visit. Blood was centrifuged for 10 min at 520 × g at 4°C to separate plasma from red blood cells and was stored at -80°C until analyzed. Fasting plasma total cholesterol, direct LDL

cholesterol, HDL-cholesterol, triglycerides concentrations were measured by a commercial lab (Alverno Laboratories, Hammond, IN). Fasting glucose concentrations were measured with a hexokinase reagent kit (Abbott, South Pasadena, CA). Fasting insulin was assessed as total immunoreactive insulin (Coat-A-Count Insulin, Los Angeles, CA). 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]. Plasma homocysteine was quantified using HPLC with fluorometric detection.

Statistical analyses

All data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS 24.0 for Windows (SPSS Inc.). A two-tailed P value of less than 0.05 was considered statistically significant. Tests for normality were included in the model, and all data were found to be normally distributed. For the sample size calculation, we estimated that the time restricted feeding group would reduce body weight by 3% by week 12. We calculated that n = 18 participants per group would provide 80% power to detect a significant difference of 3% in body weight in the time restricted feeding group by week 12, using a two-tailed independent-samples t-test with $\alpha = 0.05$. We anticipated a dropout rate of 20%. Thus, we aimed to recruit n = 23 subjects in the time restricted feeding group, assuming that n = 18 would complete the trial.

Differences between the time restricted feeding and control groups at baseline were analyzed by an independent samples t-test (continues variables) or the McNemar test (categorical variables). Data were included for 46 participants, and means were estimated using an intention-to-treat analysis using

last observation carried forward. Repeated measures two-factor ANOVA with groups (time restricted feeding and control) as the between-subject factor and time (week 1 and 12) as the within-subject factor was used to compare changes in dependent variables between the groups over time. When there was a significant main effect but no interaction, post hoc comparisons were performed using Bonferroni's correction to determine differences between group means.

4. Results

Baseline characteristics and dropouts

As portrayed in **Figure 1**, n = 23 subjects began the time restricted feeding intervention and 6 dropped out. No subjects reported dropping out of the time restricted feeding group due to issues with the diet. At baseline, there were no statistically significant differences between the time restricted feeding group and the historical control group for age, sex, ethnicity, weight, height or BMI (**Table 1**).

Table 1 Baseline characteristics[1]

	Time restricted feeding	**Control**	**P value [2]**
n	23	23	
Age (y)	50 ± 2	48 ± 2	0.43
Sex (F/M)	20/3	21/2	0.82
Ethnicity			0.69
African American	17	17	
Caucasian	3	5	
Hispanic	3	1	
Weight (kg)	95 ± 3	92 ± 3	0.34
Height (m)	1.66 ± 0.02	1.63 ± 0.01	0.29
BMI (kg/m^2)	35 ± 1	34 ± 1	0.61

[1] All values reported as mean $\pm$ SEM.

[2] P values for comparison of baseline variables between groups using independent samples t-test (continuous variables) and the McNemar test (categorical variables).

Adherence to the time restricted feeding window

Subjects in the time restricted feeding group were compliant with the prescribed eating window (10:00 to 18:00 h) on 5.6 ± 0.3 d/week (**Figure 2**), and this level of adherence did not change over the course of the trial (P = 0.86). At baseline, the time restricted feeding and control groups reported a similar mean daily eating duration of 11 ± 1 h (**Table 2**). By week 12, mean daily eating duration in the time restricted feeding group was significantly shorter (8 ± 1 h) than that of the control group (11 ± 1 h) (group × time interaction, P = 0.01). The start of the eating duration in the time restricted feeding group was later than that of the control group during the study (group × time interaction, P = 0.01), and the end of the eating duration was similar between the groups during the study (no group × time interaction, P = 0.32).

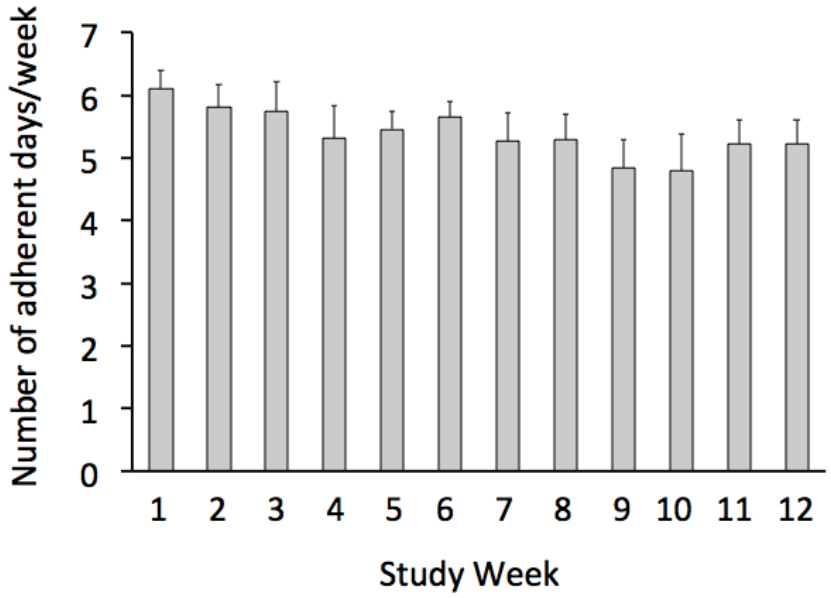

Figure 2 - Weekly adherence to the 8-hour feeding window by the time restricted feeding group[1]

[1] All values reported as mean ± SEM. Each bar indicates the mean number of days per week that the time restricted feeding subjects were compliant with the 8-hour feeding window. On average, the time restricted feeding group was compliant with the prescribed eating window (10:00 to 18:00 h) on 5.6 ± 0.3 d/week, and this level of adherence did not change over the course of the trial (P = 0.86, repeated measures ANOVA).

Dietary intake and physical activity

At baseline, energy intake was similar in the time restricted feeding and control groups (**Table 2**). During the trial, energy intake decreased in the time restricted feeding group by 341 ± 53 kcal/d relative to controls (group × time interaction, P = 0.04). Self-reported intake of macronutrients, dietary cholesterol and fiber did not differ between groups at baseline or post-treatment. Activity level, measured as steps/d, was similar at baseline in the time restricted feeding and control groups, and did not change over the course of the trial in either group.

Body weight and body composition

Body weight decreased in the time restricted group (-2.6% ± 0.5) relative to controls during the 12-week study (group × time interaction, P < 0.001) (**Figure 3**). BMI decreased in the time restricted feeding group relative to the control group during the trial (group × time interaction, P < 0.001). There were no statistically significant differences (i.e. no group × time interaction) between groups for fat mass, lean mass or visceral fat mass.

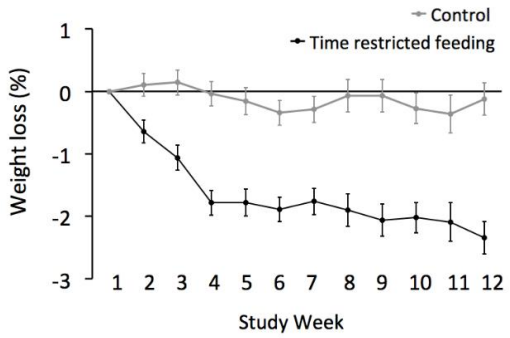

Figure 3 - Weight loss during the 12-week trial[1]

[1] All values reported as mean ± SEM. Data were included for 46 participants; means were estimated using an intention-to-treat analysis using last observation carried forward. Body weight decreased in the time restricted feeding group relative to controls over 12 weeks (P < 0.001 for time × group interaction).

Table 2 - Self-reported dietary intake, eating duration, and physical activity at baseline and week 12[1]

	Time restricted feeding (n = 23)		Control (n = 23)		P-value Time × group [3]
	Baseline [2]	**Week 12**	**Baseline** [2]	**Week 12**	
Energy (kcal)	1676 ± 114	1335 ± 162	1645 ± 113	1654 ± 191	**0.04**
Protein (%)	16 ± 1	17 ± 1	17 ± 1	17 ± 1	0.40
Carbohydrates (%)	47 ± 2	46 ± 2	46 ± 2	45 ± 2	0.61
Fat (%)	37 ± 1	37 ± 2	37 ± 1	38 ± 2	0.74
Cholesterol (mg)	279 ± 24	214 ± 27	275 ± 27	265 ± 37	0.32
Fiber (g)	16 ± 2	13 ± 1	14 ± 1	15 ± 2	0.17
Daily eating duration (h)	11 ± 1	8 ± 1	11 ± 1	11 ± 1	**0.01**
Start of eating duration (local time, h)	8:30 ± 0:30	10:00 ± 0:30	9:30 ± 0:30	8:30 ± 0:30	**0.01**
End of eating duration (local time, h)	19:30 ± 0:30	18:00 ± 0:30	20:30 ± 0:30	19:30 ± 0:30	0.32
Steps/day	6896 ± 723	7443 ± 880	6148 ± 775	6967 ± 584	0.84

[1] All values reported as mean ± SEM. Data for all variables were collected over a 7-d period at baseline (prior to the commencement of the study) and week 12 in the TRF and control groups. Data were included for 46 participants; means were estimated using an intention-to-treat analysis using last observation carried forward. [2] Baseline variables: No difference between groups for any parameter (Independent samples t-test). [3] P values reported for the time restricted feeding group relative to the control group (group × time interaction) using repeated-measures 2-factor ANOVA.

Metabolic disease risk factors

There were no differences between groups for any metabolic disease risk factor (**Table 3**). Systolic blood pressure significantly decreased in the time restricted feeding group (-7 ± 2 mm Hg) relative to controls during the study (group × time interaction, P = 0.02). There were no statistically significant differences (i.e. no group × time interaction) between groups for diastolic blood pressure, heart rate,

total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, insulin, HOMA-IR, or homocysteine.

Table 3 - Body composition and metabolic disease risk factors after 12 weeks[1]

	Time restricted feeding (n = 23)		**Control (n = 23)**		**P-value Time × group [3]**
	Baseline [2]	**Week 12**	**Baseline [2]**	**Week 12**	
Body weight (kg)	95 ± 3	92 ± 3	92 ± 3	92 ± 3	**<0.001**
Fat mass (kg) [4]	42 ± 2	40 ± 2	37 ± 2	37 ± 2	0.23
Lean mass (kg)	50 ± 2	50 ± 2	53 ± 2	53 ± 2	0.12
Visceral fat mass (kg)	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	0.19
BMI (kg/m^2)	35 ± 1	34 ± 1	34 ± 1	34 ± 1	**<0.001**
Systolic blood pressure (mm Hg)	128 ± 4	121 ± 3	123 ± 4	124 ± 3	**0.02**
Diastolic blood pressure (mm Hg)	83 ± 2	82 ± 2	81 ± 2	82 ± 2	0.41
Heart rate (bpm)	69 ± 2	71 ± 2	73 ± 2	73 ± 3	0.33
Total cholesterol (mg/dl)	177 ± 7	178 ± 9	192 ± 7	185 ± 7	0.15
LDL cholesterol (mg/dl)	108 ± 5	110 ± 7	114 ± 7	112 ± 6	0.54
HDL cholesterol (mg/dl)	48 ± 2	49 ± 2	61 ± 3	55 ± 2	0.11
Triglycerides (mg/dl) [4]	105 ± 11	93 ± 9	89 ± 7	89 ± 11	0.43
Fasting glucose (mg/dl)	79 ± 4	82 ± 2	87 ± 2	87 ± 2	0.77
Fasting insulin (uIU/ml) [4]	8.3 ± 1.0	5.7 ± 0.7	9.2 ± 1.4	10.3 ± 1.9	0.16
HOMA-IR [4]	1.6 ± 0.2	1.0 ± 0.2	2.0 ± 0.3	2.2 ± 0.4	0.21
Homocysteine (μmol/l) [4]	9.9 ± 0.6	9.0 ± 0.5	10.1 ± 0.5	9.4 ± 0.5	0.83

[1] All values reported as mean ± SEM. Data were included for 46 participants; means were estimated using an intention-to-treat analysis using last observation carried forward. HOMA-IR: Homeostatic model assessment Insulin resistance; RMR: Resting metabolic rate. [2] Baseline variables: No difference between groups for any parameter (Independent samples t-test). [3] P values reported for the time restricted feeding group relative to the control group (group × time interaction) using repeated-measures 2-factor ANOVA. [4] Significant main effect of time, $P < 0.05$.

5. Discussion

This study is the first trial to examine the impact of time restricted feeding on body weight and metabolic disease risk factors in an obese population. We show here that 12 weeks of 8-h time restricted feeding (i.e. limiting food intake to 10:00 to 18:00 h daily) decreases body weight by ~3% relative to a no-intervention historical control group. We also demonstrate that this fasting regimen produces significant reductions in systolic blood pressure relative to controls.

Adherence to the time restricted feeding window was assessed daily via self-report. Our findings show that subjects were adherent to the prescribed eating window on ~6 days per week, and that this level of adherence remained constant throughout the 12-week trial. On average, the time restricted feeding subjects reduced their daily eating duration by 3 h/d, i.e. from 11 h/d to 8 h/d. The dropout rate in the time restricted feeding group (26%) was quite high for a short-term trial. However, no one in the time restricted feeding group reported dropping out due to issues with the diet. These preliminary findings suggest that time restricted feeding may be somewhat well tolerated over short periods in obese subjects.

Our findings also indicate that reducing the daily eating window to 8-h/d decreases caloric intake by ~300 kcal/d, without intentional calorie counting. As a result of this daily energy deficit, subjects in the time restricted feeding group lost ~3% of body weight over 12 weeks, versus controls. Our body composition data suggest that the majority of this weight was lost at fat mass, with a possible retention in lean mass. The degree of weight loss demonstrated here is less than what was achieved in

the 10-h time restricted feeding study (4%) [21]. However, in the 10-h TRF adherence was measured via a real-time phone application. This may have established better adherence, further calorie restriction, and in turn greater weight loss. Our results, however, are similar to the 4-8-h time restricted feeding trials (1-3%) [22, 99]. In comparison to other forms of intermittent fasting [4, 7-9, 36, 97, 98], time restricted feeding appears to produce less weight loss. For instance, after 12 weeks of alternate day fasting or 5:2, body weight typically decreases by 4-6% from baseline [4, 7-9, 36, 97, 98]. We speculate that this difference in weight loss is due to a greater overall caloric restriction in ADF than that of TRF. TRF is strictly a time restriction and does not include calorie counting or diet modification. TRF produced a 20% daily calorie deficit, however this may even be an overestimate due to the under reporting on food records. Our group recently demonstrated via doubly labeled water that ADF and traditional caloric restriction had a greater than 35% daily energy restriction at month (10). One potential confound in the current study is the lack of an objective measure to assess eating duration. As time restricted feeding is a recent concept, methods to objectively record eating time are yet to be optimized. Self-reporting of eating duration, as used in the current study, may not be optimal. An app-based recording of all eating events among 156 healthy adults found a self-reporting error of 10% [21]. Objective methods of recording eating events also show a mean eating duration that is different from what is widely believed [21]. A study assessing eating pattern among non-shift worker adults found the median daily eating duration can be 15-h or longer, and less than 15% of adults eat for less than a 12-h duration [21]. In comparison, in the present study, the self-reported baseline eating duration was 11 h, which is likely inaccurate. Our study also permitted the consumption of low energy drinks including coffee, tea, and diet soda. These drinks contain caffeine, which is known to perturb circadian rhythm [102]. Since time restricted feeding is based on the principle of circadian rhythm

regulation of metabolism, low-energy caffeinated drinks may not count significantly towards energy consumption, but can have significant impact on circadian regulation.

Future trials in this area can be improved by using objective measures to better assess daily eating durations. It will also be of interest to investigate whether shorter eating windows (4-6 h) produce a degree of weight loss that is comparable to that of alternate day fasting and 5:2. Moreover, how the placement of the feeding window influences weight loss and adherence will also be important to examine. We chose to prescribe a feeding window of 10:00 to 18:00 h, so that the intervention would be standardized across all subjects. We assumed that this window would produce maximal adherence, as it would cause minimal disruption to the typical eating schedule (i.e. subjects could still have their breakfast in the morning, lunch in the early afternoon, and dinner in the early evening). However, recent trials [80, 103] have found that consuming larger meals earlier in the day produce better weight loss than similar sized meals consumed later in the evening. Whether weight loss and adherence can be improved by shifting the eating window earlier in the day warrants investigation.

Metabolic disease risk indicators remained relatively unaffected by the time restricted feeding regimen. Systolic blood pressure was the only parameter that improved over the course of the study, relative to controls. Reductions in insulin, insulin resistance, triglycerides, and homocysteine were also observed over time, but these effects were not statistically different from the control group. In the study by Moro et al [22], plasma lipids and inflammatory factors also remained unchanged with 8-h time restricted feeding. It is likely that the degree of weight loss produced by 8-h time restricted

feeding was not large enough to improve these outcome measures. Accumulating evidence suggests that >5% weight loss is required to improve plasma lipid concentrations and glucoregulatory factors [104]. It should also be noted that the obese subjects in the present study were metabolically healthy at baseline, i.e. their blood pressure, plasma lipid, glucose, and insulin levels were all within the normal range. Previous work indicates that intermittent fasting regimens [8, 97, 98] and other lifestyle regimens [105, 106] have little effect on cardiometabolic disease risk factors in healthy obese subjects. It will be of interest to examine whether time restricted feeding can improve these risk factors in other groups of obese patients, such as those with compromised insulin sensitivity or dyslipidemia [8, 107].

This study has several limitations. First, the study was not a randomized controlled trial. We compared the effects of time restricted feeding to a matched historical control group from a previous weight loss trial conducted by our group. The trial (REF) from which the controls were selected was conducted between 2011-2015. As such, the lapse of up to five years between trials could have influenced what the control subjects knew about weight control, and what foods were available in the marketplace due to seasonality. These issues should be considered when interpreting the present findings. In order to truly determine the effect of time restricted feeding on body weight and other metabolic disease variables, future trials should implement a randomized design where controls are enrolled concurrently. Second, the study was quite short (12 weeks). Longer-term trials will be needed to determine the degree of weight loss that can be achieved with time restricted feeding. Third, adherence and dietary intake were assessed by self-report, thus our estimates of eating duration and caloric deficit may be inaccurate [108, 109]. Implementing mobile apps to assess adherence in real-time [21] will help determine how well subjects can adhere to the prescribed eating window. Fourth,

our study involved only metabolically healthy obese subjects, so our findings cannot be generalized to other population groups.

In summary, these findings suggest that 8-h time restricted feeding produces mild caloric restriction and weight loss in obese adults, without intentional calorie counting. This diet may also offer some clinical benefit by reducing systolic blood pressure. These preliminary data offer promise for the use of time restricted feeding as a weight loss technique in obese adults, but longer-term, larger-scale randomized controlled trials will be required before solid conclusions can be reached.

6. Acknowledgments

KG designed the research, conducted the clinical trial, analyzed the data, performed the statistical analysis, and wrote the manuscript; KKH, NH, JS, CMK, and JFT assisted with the conduction of the clinical trial; SP assisted with data interpretation and wrote the manuscript; KAV designed the research, analyzed the data, wrote the manuscript, and had primary responsibility for final content.

IV. MANUSCRIPT 2

Safety of 8-h time restricted feeding in adults with obesity

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1. Abstract

This study examined the safety of time restricted feeding (TRF; 8-h feeding window/16-h fasting window daily) in obese adults. Twenty-three subjects participated in an 8-h TRF intervention for 12 weeks. Self-reported adverse events, body image perception, complete blood count and disordered eating patterns did not change from baseline to week 12. These findings suggest that consuming food within an 8-h window can safely facilitate weight loss in subjects with obesity.

Key Words: Intermittent fasting, time restricted feeding, weight-loss, safety, adverse events, obese adults

2. Introduction

Intermittent fasting regimens involve periods fasting followed by periods of eating freely. The most common forms of intermittent fasting are alternate day fasting (500 calorie fast days alternated with ad libitum feast days) and the 5:2 diet (two 500 calorie fast days and 5 ad libitum feast days per week). Time restricted feeding (TRF) is a newer form of intermittent fasting. TRF involves shortening the eating window to 4-10 hours each day. The most common form of TRF is 16:8 during which subjects consume all food within 8 hours and water fast during the remaining 16 hours. Accumulating evidence suggests that TRF is an effective means of decreasing body weight while maintaining lean mass in normal weight and overweight subjects [21, 22, 99]. More recently, it's been shown that TRF may also be effective for weight loss in adults with obesity [110]. Although TRF appears to have beneficial effects on body weight, the safety of this diet has been questioned. For instance, increased frequency of constipation, irritability and fatigue are common safety concerns with all forms intermittent fasting ([26]. Additionally, consistent dietary restriction has been postulated to increase disordered eating behaviors [56-58]. Accordingly, this study was undertaken to determine the effects of TRF on certain safety parameters, including: eating disorder symptoms, body image perception, complete blood count, and frequency of adverse events, in adults with obesity. We hypothesized that TRF would not negatively impact any of these parameters during the 12-week trial.

3. Methods

Subject selection

This 12-week study is a secondary analysis of a larger study [110]. The University of Illinois Chicago Office for the Protection of Research Subjects approved the experimental protocol, and all research participants gave their written informed (IRB approval #2016-0119). Subjects were recruited from September 2016 to January 2017 from the Chicago area via advertisements placed around the University of Illinois Chicago campus. A total of 40 subjects were consented and assessed for eligibility. Of these 40 subjects, 11 subjects were excluded because they did not meet one or more inclusion criteria, and 6 subjects declined to participate after qualifying. Twenty-three subjects began the study. Inclusion criteria were as follows: BMI between 30 and 45 kg/m^2; age between 25 and 65 years; pre-menopausal or post-menopausal (absence of menses for more than 2 years); sedentary to moderately active (<7500 steps/d); weight stable for 3 months prior to the beginning of the study (< 4 kg weight loss or weight gain); non-diabetic; no history of cardiovascular disease (myocardial infarction or stroke); non-smoker; not a shift worker; and not taking weight loss, lipid- or glucose-lowering medications.

Study design and time restricted feeding protocol

To test the study objectives, a single-arm trial consisting of a 2-week baseline period followed by a 12-week TRF intervention period was implemented. During the baseline period, subjects were asked to continue with their usual diets and keep their weight stable. During the 12-week intervention period, subjects were instructed to eat ad libitum within an 8-h window (10:00 to 18:00 h daily), and fast from

18:00 to 10:00 h daily. During the 8-h feeding window, there were no restrictions on the type or quantity of foods consumed. Subjects were not required to monitor caloric intake during the ad libitum feeding period. During the fasting period, subjects were encouraged to drink plenty of water and were permitted to consume calorie-free beverages, such black tea, coffee, and diet sodas.

Body weight, resting metabolic rate, activity and food intake

Body weight was assessed at the beginning of every week to the nearest 0.25 kg using a balance beam scale (HealthOMeter, Boca Raton, FL) at the research center. Resting metabolic rate (RMR) was measured by a handheld open circuit indirect calorimeter in between the 6:00 and 9:00 h (MedGem Indirect Calorimeter, Microlife, USA) at the research center. Subjects were instructed to abstain from food, drink, and exercise for 12 h prior to the visit. Timing since the last meal (12 h) was standardized for each subject prior to the RMR measurement. Subjects first rested in a dark room in the supine position for 15 min, then a mouthpiece and nose clip were placed on the subject, and oxygen consumption was measured until it reached a stable flow (approx. 10 min). Subjects were instructed to maintain their activity level throughout the trial. Step counts were measured over 7-d during the baseline period and at week 12 by a pedometer (Yamax Digi-walker SW-200, Yamax Inc., San Antonio, TX). Intake of energy, macronutrients and timing of food consumption was assessed by a 7-d food record at baseline and week 12 and analyzed by Nutritionist Pro software (Axxya, Stafford, TX).

Adverse event, eating disorder, body image, and eating behavior questionnaires

All questionnaires were administered at baseline (2 weeks prior to the TRF intervention), week 1 (first day of TRF intervention), and after 12 weeks of the TRF. Gastrointestinal and neurological issues were assessed by an adverse events questionnaire. Eating disorder symptoms were measured using the Multidimensional Assessment of Eating-Disorder Symptoms (MEADS) [59]. This validated self-report inventory measures six symptom domains related to eating disorders, including: binge eating, restrictive eating, purgative behaviour, fear of fatness, avoidance of forbidden foods, and depression. Body image was assessed by the Body Shape Questionnaire (BSQ) [66]. The BSQ is a validated questionnaire that measures excessive concern about one's body size and shape [66]. Higher scores on the BSQ indicate greater concerns with body size and shape. Dietary restraint, uncontrolled eating, and emotional eating were assessed by the validated three-factor eating questionnaire (TFEQ) [67].

Complete blood count and ketones

Twelve-h fasting blood samples were collected between 5:00 and 9:00 h at baseline, week 1, and week 12. The subjects were instructed to avoid exercise, alcohol, and coffee for 24 h before each visit. Blood was centrifuged for 10 min at 520 × g at 4°C to separate plasma from red blood cells and was stored at -80°C until analyzed. Complete blood counts were performed using a BC-5500 automatic blood cell analyzer, and the ketone, β-hydroxybuterate, was measured by the biosensor method (Medisense Precision Xtra, Abbott, Bedford, MA).

Statistical analyses

All data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS 24.0 for Windows (SPSS Inc., Chicago, IL). Tests for normality were included in the model, and all data were found to be normally distributed. ANOVA was used to assess changes in continuous variables over time. McNemar's test was used to assess changes in categorical variables over time. Data were included for the 23 participants who began the study, and means were estimated using an intention-to-treat analysis using last observation carried forward. A two-tailed P value of less than 0.05 was considered statistically significant.

4. Results

Body weight, resting metabolic rate, activity, and food intake

Body weight significantly ($P < 0.001$) decreased by 2.6 ± 0.5% after 12 weeks of TRF. Resting metabolic rate did not change over time (baseline: 1431 ± 62 kcal/d; week 1: 1393 ± 82 kcal/d; week 12: 1318 ± 61 kcal/d). Activity level did not change from baseline (6896 ± 723 steps/d) to week 12 (7443 ± 880 steps/d). Before starting the TRF intervention, subjects typically started eating at 8:30 ± 0:30 h:min and finished eating by 19:30 ± 0:30 h:min. Energy intake decreased ($P < 0.05$) from baseline (1676 ± 114 kcal/d) to week 12 (1335 ± 162 kcal/d). There were no changes over the course of the trial in percent energy intake from protein (baseline: 16 ± 1%; week 12: 17 ± 1%), carbohydrates (baseline: 47 ± 2%; week 12: 46 ± 2%) or fat (baseline: 37 ± 1%; week 12: 37 ± 2%).

Table 4 - Self-reported adverse events after 12 weeks of time restricted feeding -

Adverse events	Baseline	Week 1	Week 12	P-Value
Gastrointestinal				
Nausea	0%	0%	6%	1.00
Vomiting	0%	0%	0%	1.00
Diarrhea	0%	0%	12%	1.00
Constipation	17%	29%	24%	1.00
Bad Breath	18%	14%	12%	0.50
Dry Mouth	32%	14%	12%	0.13
Neurological				
Dizziness	9%	0%	18%	1.00
Weakness	14%	0%	6%	0.50
Headache	32%	24%	24%	0.50
Fatigue	14%	10%	12%	1.00
Irritability	23%	19%	6%	0.25
Unhappiness	14%	14%	0%	1.00

Values reported as mean % occurrences at each time point (baseline n = 23; week 1 n = 23; week 12 n = 17). Baseline values were measured 2 weeks before the start of the intervention (week 1). P-value: McNemar's test.

Adverse events, eating disorder symptoms, body image, and eating behaviors

Self-reported adverse events (gastrointestinal or neurological) did not change over time (**Table 1**). Eating disorder symptoms including depression, binge eating, purgative behavior, fear of fatness, restrictive eating, and avoidance of forbidden foods, did not change from baseline to week 12 (**Table 2**). Concerns about body size and shape remained unchanged (**Table 2**). Food intake behavior such as cognitive restraint, uncontrolled eating and emotional eating did not change over time (**Table 2**).

Complete blood count and ketones

There were no significant changes in any of the complete blood count parameters over time (**Table 3**). Beta-hydroxybuterate also remained unchanged over the course of the study (baseline: 1.0 ± 1.1 mmol/L; week 1: 0.9 ± 0.4 mmol/L; week 12: 1.2 ± 1.2 mmol/L).

Table 5 - Eating disorder symptoms, body shape perception, and eating behaviors after 12 weeks of time restricted feeding

	Baseline	Week 1	Week 12	P-Value
Eating disorder symptoms				
Depression	32 ± 1	32 ± 1	32 ± 1	0.90
Binge Eating	28 ± 2	27 ± 1	27 ± 1	0.79
Purgative behavior	13 ± 1	11 ± 1	12 ± 1	0.23
Fear of fatness	41 ± 2	39 ± 2	41 ± 2	0.89
Restrictive eating	28 ± 2	27 ± 2	29 ± 2	0.68
Avoidance of forbidden foods	37 ± 2	38 ± 2	38 ± 2	0.93
Body image perception				
Concerns about body size/ shape	47 ± 3	46 ± 3	47 ± 3	0.96
Eating behaviors				
Dietary restraint	17 ± 1	16 ± 1	17 ± 1	0.51
Uncontrolled eating	18 ± 1	18 ± 1	18 ± 1	0.89
Emotional eating	7 ± 1	7 ± 1	6 ± 1	0.96

Values reported as mean ± SEM (baseline n = 23; week 1 n = 23; week 12 n = 17). Baseline values were measured 2 weeks before the start of the intervention (week 1). P-value: ANOVA.

5. Discussion

This study is the first to show that TRF is a safe diet therapy for weight loss as it does not negatively impact eating disorder symptoms, eating behaviors, or measures of overall health, such as complete blood count. Moreover, no gastrointestinal or neurological adverse events were reported with 12 weeks of TRF.

It has been speculated that fasting or calorie restriction may increase eating disorder symptoms. However, recent findings suggest that this is not the case. For instance, in a previous trial [111], daily calorie restriction did not increase eating disorder symptoms and had no harmful psychological effects. Likewise, alternate day fasting has been shown to have no negative impact on eating disorder symptoms in adults with obesity [26]. Indeed, alternate day fasting may have beneficial effects by increasing dietary restraint and improving body image perception [26, 61].

Table 6 - Complete blood count after 12 weeks of time restricted feeding

	Normal range	Baseline	Week 1	Week 12	P-value
White cell count (K/UL)	5-10	5.7 ± 0.7	5.1 ± 0.5	5.1 ± 0.4	0.70
Red cell count (M/UL)	4.2-6.1	4.3 ± 0.2	4.4 ± 0.1	4.4 ± 0.1	0.91
Hemoglobin (g/dL)	12-18	12.5 ± 0.2	12.6 ± 0.2	12.6 ± 0.3	0.95
Hematocrit (%)	37-52	38.1 ± 1.3	38.0 ± 0.7	38.5 ± 0.9	0.99
Mean corpuscular volume (FL)	80-100	89.3 ± 5.1	88.0 ± 2.4	87.8 ± 1.9	0.87
Mean corpuscular hemoglobin (pg)	27-32	29.4 ± 1.6	29.2 ± 0.9	29.1 ± 0.7	0.93
Mean corpuscular hemoglobin concentration (%)	32-36	32.9 ± 0.6	33.1 ± 0.3	33.1 ± 0.2	0.95
Red blood cell distribution (%)	11-15	14.4 ± 0.5	13.8 ± 0.3	13.9 ± 0.3	0.69
Platelet count (K/UL)	150-450	202.7 ± 12.8	218.8 ± 8.8	212.1 ± 9.9	0.61
Neutrophil (%)	35-80	56.3 ± 5.6	49.8 ± 3.0	51.9 ± 4.9	0.45
Lymphocyte (%)	18-44	32.3 ± 4.7	38.5 ± 4.2	35.8 ± 3.1	0.47
Monocyte (%)	4.7-12.5	7.2 ± 1.5	7.5 ± 0.6	7.5 ± 0.7	0.96
Eosinophil (%)	0-4	3.7 ± 1.2	3.6 ± 0.6	3.5 ± 0.6	0.99
Basophil (%)	0-1.2	0.8 ± 0.2	0.7 ± 0.2	1.1 ± 0.2	0.27
Neutrophil count (K/UL)	1.8-7.7	3.3 ± 0.6	2.7 ± 0.4	2.8 ± 0.3	0.59
Lymphocyte count (K/UL)	0.8-4.8	1.7 ± 0.3	1.9 ± 0.2	1.8 ± 0.2	0.67
Monocyte count (K/UL)	0.2-0.9	0.4 ± 0.0	0.4 ± 0.0	0.4 ± 0.0	0.94
Eosinophil count (K/UL)	0.0-0.8	0.2 ± 0.1	0.2 ± 0.0	0.2 ± 0.0	0.68
Basophil count (K/UL)	0-0.1	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.39

Values reported as mean ± SEM (baseline n = 23; week 1 n = 23; week 12 n = 17). Baseline values were measured 2 weeks before the start of the intervention (week 1). P-value: ANOVA.

In the present trial, no significant increase in adverse events was reported with 12 weeks of TRF. These results are in line with what has been shown with alternate day fasting. For instance, 8-weeks alternate day fasting did not increase the frequency of gastrointestinal events (constipation, diarrhea, water retention or bad breath) in adults with obesity [26]. Rates of dizziness, general weakness, or sleep disturbances also did not increase with alternate day fasting [26]. The present trial also demonstrates no change in complete blood count with TRF. Similarly, in a previous trial [40], complete blood count did not change when normal weight adult subjects were required to consume all of their food within a

4-h period each day. Taken together, these findings suggest that TRF regimens are well tolerated by normal weight and obese adults.

There are several limitations to our study. First, we had a small sample size (n = 23) which limits our ability to detect a significant difference from pre- to post-treatment for many variables, most notably RMR (effect size = 0.25). Second, we did not utilize a control group. Third, our adverse events questionnaire is not very comprehensive. A more elaborate list of adverse events should be developed to more accurately examine the safety TRF. Fourth, using the MedGem to assess RMR is a limitation as this tool has been shown to overestimate RMR when compared to a traditional indirect calorimeter [112]. The MedGem is also limited in that it does not provide measures of respiratory ratio. Fifth, our study was short (12 weeks). Longer-term studies will be needed to examine how these measures of safety change over time.

In summary, these pilot findings suggest that TRF is a safe diet therapy for weight loss. TRF did not have any negative impact on eating disorder symptoms, body image perception, or eating behaviors. No adverse events were reported during the study, and blood chemistry remained unaffected. These findings offer promise for the use of TRF as a safe lifestyle intervention for weight loss in adults with obesity. However, longer-term trials that implement larger cohorts are required to confirm these preliminary results.

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V. MANUSCRIPT 3

Effect of 8-hour time-restricted feeding on sleep quality and duration in adults with obesity

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Running head: Time restricted feeding and sleep

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1. Abstract

This study examined the effects of time restricted feeding (TRF; 8-h feeding window/16-h fasting window daily) on sleep. Obese adults (n = 23) followed 8-h TRF for 12 weeks. Pittsburgh Sleep Quality Index (PSQI) total score was below 5 at week 1 (4.7 ± 0.5) and week 12 (4.8 ± 0.7) indicating good sleep quality throughout the trial. Subjective measures of wake time, bedtime, and sleep duration remained unchanged. Findings from this secondary analysis indicate that TRF does not alter sleep quality or duration in subjects with obesity.

2. Introduction

Only 35% of adults meet the recommended 7-9 h of sleep each night [71]. Obesity is associated with poor sleep quality and shorter sleep duration [27-29]. Weight loss by means of dietary restriction may help improve sleep quality and quantity [73, 74]. Time-restricted feeding (TRF) is an intermittent fasting weight-loss strategy, which involves an ad libitum feeding window of 4-10 h and a fasting window 14-20 h per day [113]. Evidence from animal studies suggests that TRF lowers body weight in a way that may improve circadian rhythmicity and sleep [77]. In humans, it's been shown that 10-h TRF resulted in 4% weight loss and improved sleep in overweight participants over 16 weeks [21]. Whether the same beneficial effects on body weight and sleep would occur in individuals with *obesity*, remains unknown. Accordingly, this study examined the effects of 8-h TRF on body weight, sleep quality and duration in adults with obesity. We hypothesized that 12 weeks of TRF would increase sleep quality and duration, and that these improvements would be more pronounced in subjects who were poor sleepers at baseline.

3. Methods

Subject selection

This is a secondary analysis of a 12-week study examining the effects of TRF on body weight and metabolic disease risk [114]. Subjects were recruited from the Chicago area by flyers placed around the University of Illinois Chicago campus. Inclusion criteria were as follows: BMI 30-45 kg/m^2; age 25-65 y; sedentary to moderately active (<7500 steps/d); weight stable for 3 months prior to the beginning of the study (< 4 kg weight loss or weight gain); non-diabetic; no history of cardiovascular disease (myocardial infarction or stroke); non-smoker; not a shift worker; and not taking weight loss, lipid- or glucose-lowering medications. A total of 40 subjects were assessed for eligibility, 11 subjects were excluded because they did not meet one or more inclusion criteria, and 6 subjects declined to participate after qualifying. At total of 23 subjects began the trial and 6 dropped out by week 12. 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

The trial consisted of a 2-week baseline period followed by a 12-week TRF intervention period. During the baseline period, subjects were asked to remain weight stable by continuing their regular diet and exercise routines. During the 12-week TRF intervention, subjects were instructed to eat ad libitum from 10:00 to 18:00 h daily, and fast from 18:00 to 10:00 h daily. During the 8-h feeding window, there were no restrictions on types or quantities of foods consumed and subjects were not required to monitor calorie intake. During the 16-h fasting period, only water and calorie-free beverages, such black tea,

coffee, and diet sodas, were permitted.

Body weight, physical activity, and diet compliance

Body weight was assessed using a balance beam scale (HealthOMeter, Boca Raton, FL) at the beginning of each week at the research center. Body composition (fat mass, lean mass, visceral fat mass) was measured using dual x-ray absorptiometry (DXA; iDXA, General Electric Inc). Compliance to the 8-h TRF window was measured using a daily adherence log, which recorded the time that the subjects started and stopped eating each day. The day was coded as "adherent" if the subject consumed food only within the 8-h window (10:00 to 18:00 h), and "not adherent" if the subject consumed food outside of this window. Total percent compliance was calculated as: number of days adherent / total number of days in the trial x 100. Subjects were asked to maintain their current level of physical activity throughout the trial. Changes in physical activity were assessed by a pedometer (Yamax Digi-walker SW-200, Yamax Inc., San Antonio, TX) over a 7-d period at the beginning and end of the study.

Sleep measures

All questionnaires were administered at the beginning of the baseline period, on the first day of the intervention (week 1) before the diet commenced, and at week 12. The severity of insomnia in the past week was measured by the Insomnia severity index (ISI), which is a 7-item questionnaire [115]. 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 was measured by the Pittsburgh Sleep Quality Index (PSQI) [116]. This 19-item self-report questionnaire 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 asks for usual bedtime, usual wake time, and hours of actual obtained sleep, which were also analyzed in the study. Risk of obstructive sleep apnea was estimated using the Berlin Questionnaire at baseline [117].

Statistical analyses

All data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS 25.0 for Mac (SPSS Inc.). $P < 0.05$ was considered statistically significant. Data were included for the 23 participants who began the study, and means were estimated using an intention-to-treat analysis using last observation carried forward. One-way ANOVA with Tukey's post-hoc test was used to assess changes in continuous variables between baseline, week 1 and week 12. Paired t-test was used to assess changes between week 1 and 12. We also performed a sub-analysis to examine the effects of the TRF intervention in "good sleepers" and "poor sleepers". Good sleepers were subjects with PSQI total score equal to or below 5 at baseline (n = 13) and poor sleepers were subjects with a PSQI total score greater than 5 at baseline (n = 10).

4. Results

Body weight, physical activity, and diet compliance

In "all subjects" (n = 23), body weight and fat mass were reduced ($P < 0.01$) after 12 weeks of TRF (**Table 1**). Reductions ($P < 0.05$) in body weight and fat mass were also observed in "good sleepers" (n = 13) and "poor sleepers" (n = 10) by the end of the study. Lean mass and visceral fat mass did not change over the course of the trial in any group. "All subjects" complied with the 8-h TRF window on 80% of days during the 12-week study (**Table 1**). "Good sleepers" were adherent with 8-h feeding window on 83% of days, and poor sleepers were adherent 76% of days. Physical activity, measured as steps/d, did not change over the course of the trial in any group (**Table 1**).

Table 7 - Body weight, body composition, and sleep variables after 12 weeks of time restricted feeding

	All Subjects (n = 23)			**Good sleepers (n = 13)**			**Poor sleepers (n = 10)**		
	Baseline	**Week 1**	**Week 12**	**Baseline**	**Week 1**	**Week 12**	**Baseline**	**Week 1**	**Week 12**
Demographics									
Age	50 ± 2	--	--	49 ± 2	--		51 ± 3	--	
Sex (Female/Male)	20 / 3	--	--	12 / 1	--		8 / 2	--	
Anthropometrics									
Body weight (kg)	95 ± 3 [a]	95 ± 3 [a]	92 ± 3 [b]	93 ± 4 [a]	93 ± 4 [a]	90 ± 4 [b]	101 ± 5 [a]	101 ± 5 [a]	99 ± 5 [b]
Fat mass (kg)	--	42 ± 2	40 ± 2*	--	40 ± 3	38 ± 3*	--	44 ± 3	42 ± 3*
Lean mass (kg)	--	50 ± 2	50 ± 2	--	49 ± 2	48 ± 2	--	52 ± 3	52 ± 3
Visceral fat mass (kg)	--	1.2 ± 0.1	1.1 ± 0.1	--	1.0 ± 0.1	1.0 ± 0.1	--	1.5 ± 0.1	1.3 ± 0.2
Compliance with diet (%)	--	--	80 ± 4	--	--	83 ± 4	--	--	76 ± 8

Steps/d	--	6896 ± 723	7443 ± 880	--	6324 ± 998	7212 ± 1483	--	7533 ± 1069	7700 ± 957
Insomnia severity index (ISI)									
Total score	6.2 ± 1.0	5.2 ± 0.9	5.3 ± 0.9	3.9 ± 1.1	2.5 ± 0.5	2.5 ± 0.6	9.1 ± 1.1	8.6 ± 1.2	9.0 ± 1.3
Pittsburgh Sleep Quality Index (PSQI)									
Total score	4.9 ± 0.5	4.7 ± 0.5	4.8 ± 0.7	3.5 ± 0.4	3.5 ± 0.4	2.9 ± 0.4	7.6 ± 0.7	6.3 ± 0.8	7.2 ± 1.0
Wake time (h:min)	6:05 ± 0:15	5:50 ± 0:20	6:05 ± 0:15	6:30 ± 0:25	5:40 ± 0:25	6:30 ± 0:20	6:00 ± 0:25	6:00 ± 0:20	6:00 ± 0:25
Bedtime (h:min)	22:35 ± 0:20	22:30 ± 0:20	22:35 ± 0:20	22:30 ± 0:25	22:30 ± 0:20	22:30 ± 0:20	22:55 ± 0:40	22:35 ± 0:30	22:55 ± 0:40
Sleep duration (h)	7.5 ± 0.2	7.7 ± 0.2	7.9 ± 0.2	8.0 ± 0.3	7.2 ± 0.2	8.0 ± 0.1	6.9 ± 0.3	7.3 ± 0.4	6.9 ± 0.3
Berlin questionnaire									
High risk of obstructive sleep apnea (%)	32%	--	--	23%	--		44%	--	

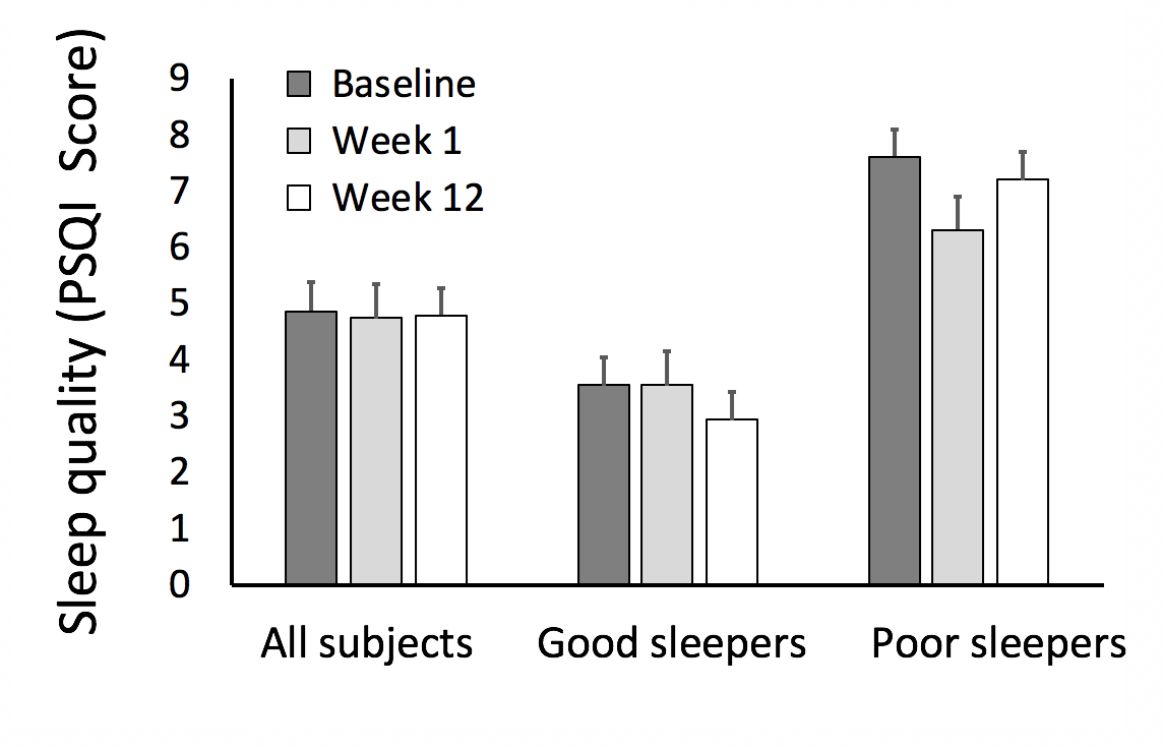
Values reported as mean ± SEM. [1] Paired t-test comparing baseline to week 12 values for "All subjects". [2] Repeated measures ANOVA (group × time interaction) comparing subjects who achieved ">3% weight Loss" versus subjects who achieved "<3% weight Loss".

Sleep

Results from the ISI survey indicate an absence of clinically significant insomnia (ISI score 0-7) in "all subjects" and "good sleepers" at baseline, week 1 and 12 (**Table 1**). "Poor sleepers", in contrast, displayed sub-threshold insomnia (ISI score 8-14) at baseline, with no significant difference by week 1 or 12. Sleep quality was measured by the PSQI questionnaire (**Figure 1**). At baseline, PSQI total score was below 5 in "all subjects" and "good sleepers" indicating no sleep disturbance issues. PSQI score did not change significantly after 12 weeks of TRF in "all subjects" and "good sleepers". PSQI total score

was greater than 5 in “poor sleepers” at baseline, indicating sleep disturbance issues at the beginning of the trial. PSQI score did not change significantly after 12 weeks of TRF in “poor sleepers”. 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 32% of “all subjects”, 23% of “good sleepers” and 44% of “poor sleepers” at baseline (**Table 1**).

Figure 4 - Sleep quality after 12 weeks of time restricted feeding



Values reported as mean ± SEM. Pittsburgh Sleep Quality Index (PSQI) questionnaire.

“All subjects” represents the group of subjects as a whole (n = 23). Subjects were then divided into groups based on baseline sleep quality: “Good sleepers” (n = 13) are subjects with a PSQI total score equal to or below 5 at baseline and “Poor sleepers” are subjects with a PSQI total score greater than 5 at baseline (n = 10). There were no statistically significant changes between baseline, week 1, and 12 in any group

5. Discussion

This study is the first to assess the effects of 8-h TRF on sleep in adults with obesity. Our findings suggest that TRF has no effect on sleep quality, timing, duration, or insomnia severity after 12 weeks of intervention. We also performed a sub-analysis to examine if poor sleepers would see greater improvements in sleep. Results reveal no improvements in sleep quality, timing or duration in poor sleepers by TRF.

Accumulating evidence suggests that nighttime eating is associated with reduced sleep duration and poor sleep quality [118, 119]. Thus, we hypothesized that an 8-h TRF intervention, that requires subjects to stop eating by 18:00 h every day, would result in improved sleep in subjects with obesity. Contrary to our hypothesis, we did not observe any improvements in sleep after 12 weeks of TRF. It is possible, however, that no benefits were seen as our cohort had good sleep quality at baseline (i.e. PSQI score less than 5) [116]. Additionally, our participants had a mean sleep duration of 7.5 h at baseline, which is in line with the recommended 7 h minimum stipulated by the National Sleep Foundation [120]. Bearing this in mind, we performed a sub-analysis to examine if TRF would improve sleep in subjects with *poor* sleep habits at baseline. Interestingly, no improvements in sleep quality, timing or duration were noted in this subgroup of poor sleepers. It should be noted that the group of poor sleepers only had mild disturbances in sleep based on PSQI and ISI scores [116] ([115]. It will be of interest for future studies in this field to examine whether TRF can improve sleep in individuals with severe insomnia and persistent sleep disturbances.

Our study has several limitations. First, we had a small sample size (n = 23). Since our power calculation was based solely on body weight, it is likely that this study was not powered adequately to identify significant changes in sleep quality, timing or duration. However, our findings can serve as pilot data to inform future studies that examine the impact of TRF on sleep. Second, this intervention was not a randomized control trial. Future studies should implement a control group to determine if TRF improves sleep to a greater extent than subjects receiving no intervention. Third, we did not implement the morningness-eveningness questionnaire (MEQ) [121] to assess the choronobiology of our subjects at baseline. Last, all measures of sleep were given by self-report. This study would have benefitted from using wrist actigraphy to provide more objective assessments of rest-activity patterns.

In summary, these preliminary findings suggest that TRF does not impact sleep quality, timing and duration in obese subjects with healthy habits at baseline. TRF also displayed no benefits in the subgroup of individuals with poor sleep habits at baseline. Although our study showed no positive effects, it's important to note that TRF did not have any negative effects on sleep in this population group (i.e. sleep quality did not get worse, and sleep duration was not shortened). Thus, TRF can be viewed as an effective weight loss strategy that has no negative impact on sleep habits in subjects with obesity.

6. Acknowledgements

This study received funding from the University of Illinois Chicago Campus Research Board Pilot Grant.

VI. DISCUSSION

1. Aim 1: The effect of 8-h TRF on body weight and body composition in adults with obesity

This is the first trial to examine the effect of 8-h TRF in subjects with obesity. We show that 12 weeks of 8-h TRF significantly decreases body weight by ~3% relative to a historical control group. Our findings also indicate that 8-h TRF elicits a natural caloric restriction of about ~350kcal/day. No changes were seen in fat mass loss, fat-free mass loss or visceral fat mass relative to the historical controls over 12 weeks. Adherence to the 8-h TRF intervention was assessed via self-report. Our findings show that subjects were adherent to the diet ~6 days per week and this remained consistent throughout the 12-week trial. It appears that adherence to 8-h TRF may be higher than in other forms of intermittent fasting, however these diets would need to be directly compared to make that assertion. On average subjects reduced their eating window by 3 h/d (i.e. from 11 h/d at baseline to 8 h/d during the TRF intervention). While our dropout rate was high (26%), no subjects dropped out due to issues with the diet, which bodes well for the use of TRF longer-term.

2. Aim 2: The effect of 8-h TRF on metabolic disease risk factors

Systolic blood pressure was reduced by 7 mm Hg (-5%) after 12 weeks of 8-h TRF. However, no other changes in metabolic disease risk factors were observed. It is possible that this group of subjects did not achieve enough weight loss to see improvements in other metabolic risk factors. Reductions in plasma lipids and glucoregulatory factors are generally only observed with >5% weight loss. Furthermore, subjects were metabolically healthy at baseline. Accumulating evidence suggests that intermittent fasting and other lifestyle regimens may have little effect on metabolic disease risk factors in healthy adults with obesity [3, 8, 97]. A longer-term TRF intervention should be completed in order

to assess if this diet could produce clinically significant weight loss in order to improve these metabolic disease risk factors.

3. Aim 3: The effect of 8-h TRF on sleep quality and duration

Our study was the first to examine the effect of 8-h TRF on sleep quality and duration. Our findings suggest that 8-h TRF has no effect on sleep quality, timing, duration, or insomnia severity after 12 weeks of intervention in subjects with obesity. However, on average, our subjects were "good" sleepers at baseline (PSQI score above 5), which may have dampened the effect of the diet on sleep improvement. Therefore, we did a sub-analysis of "good" sleepers versus "poor" sleepers to see if these groups would react differently to TRF. No differences between groups were observed in sleep quality, timing, duration, or insomnia severity. However, our study was powered for body-weight change and may not have been powered to determine change in sleep parameters. It is also important to note that no negative effects on sleep quality or duration was seen after intervention. Thus, TRF can be viewed as an effective weight loss strategy that has no negative effect on sleep quality or duration in subjects with obesity.

4. Aim 4: The safety of 8-h TRF in adults with obesity

This is the first study to examine the safety of 8-h TRF. Our findings suggest that TRF is a safe diet therapy that does not negatively affect eating disorder symptoms, eating behaviors, or measures of overall health such as resting metabolic rate and complete blood count. Furthermore, no gastrointestinal or neurological adverse events were reported after 12 weeks of intervention. These

finding suggest that TRF is a safe diet therapy for weight loss in subjects with obesity. However, longer-term trials with larger cohorts will be needed to confirm these findings.

VII. Future Directions

Future studies in this area should examine the effectiveness of long-term 8-h TRF compared to other forms of intermittent fasting. Results from the present study indicate that TRF results in only mild weight loss (3%) after 12 weeks. Other forms of intermittent fasting, such as ADF, produce greater weight loss (4-7%) in the same time frame. It will be of interest to perform a head-to-head comparison of TRF versus ADF on body weight and other metabolic disease risk factors in adults with obesity. Comparing the tolerability and degree of dietary adherence that is achieved with TRF versus ADF in a longer-term (24-52 weeks) randomized controlled trial, is of great interest.

A 6-h feeding window is another popular form of TRF, though very few studies exist to date [24, 25]. A trial comparing the effectiveness of 8-h vs 6-h TRF on body weight and metabolic disease risk markers should be performed. It will be interesting to see if compliance with the 6-h eating window is similar to that of the 8-h eating window. The degree of calorie restriction and weight loss that is produced by 6-h TRF versus 8-h TRF is also of interest. It is speculated that the shorter eating window will produce even greater calorie restriction, more pronounced weight loss, and potentially, improvements in various metabolic disease risk factors (blood pressure, triglycerides, and insulin resistance).

The ideal placement of the 8-h TRF window is another question that should be examined. Insulin sensitivity is highest in the morning [122]. As such, placing the TRF window earlier in the day may have a greater impact on glucoregulatory factors. A future study that directly compares an early 8-h TRF

regimen (e.g. 8:00 am to 16:00 h) to a late 8-h TRF regimen (e.g. 12:00 pm to 20:00 h) on body weight, fasting insulin, fasting glucose and insulin sensitivity would be highly valuable to the field.

VIII. Conclusion

In summary, these findings suggest that 8-h TRF produces mild caloric restriction and weight loss in adults with obesity, without intentional calorie counting. Adherence remained high throughout the study, and very few adverse events were reported. Moreover, TRF does not appear to have any negative effects on eating disorder symptoms, body image perception, or sleep quality and duration. As for metabolic disease risk, only blood pressure was improved. However, since the subjects in this trial were all metabolically healthy at baseline, this may have limited our ability to observe any changes in these risk factors. These preliminary data offer promise for the use of time-restricted feeding as a weight-loss technique in adults with obesity, but longer-term, larger-scale randomized controlled trials will be required before solid conclusions can be reached.

IX. APPENDICIES

APPENDIX A - CONSENT FORM

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

Time restricted feeding for weight loss, weight maintenance and cardio-protection

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: 773-610-5573
Sponsor: UIC CRB grant (Pending)

Why am I being asked?

You are being asked to be a subject in a research study about time restricted feeding for weight loss, weight maintenance, and heart disease risk reduction. 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 (eating all food between 10am-6pm) on body weight and heart disease risk factors.

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 28 times over the next 28 weeks. Each of those visits will take about 20-60 minutes. However the first and 16th visit may take 6 hours.

The 28-week study is broken down into:

- **4-week baseline period** (you will maintain your weight during this period and the amount of energy you burn on a daily basis will be measured)
- **12-week weight loss period** (you may lose weight during this period if you are assigned to the Time Restricted Feeding group or the Calorie Reduction group)
- **12-week weight maintenance** period (you will maintain your weight loss by receiving dietary counseling if you are in the Time Restricted Feeding group or the Calorie Reduction group)

APPENDIX A - CONSENT FORM - (continued)

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. You will also undergo a urine pregnancy test to make sure you are not pregnant.

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. **Time restricted feeding group:** If you fall in this category you will be asked to consume food only between the hours of 10am and 6pm each day. Before 10am and after 6pm you will only be permitted to drink water.
2. **Calorie reduction group:** Calorie reduction involves cutting down your food intake by a certain amount on a daily basis. If you fall in this category you will be asked to cut your food intake down by 25% each day. You can eat whenever is convenient for you during the day.
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 or calorie reduction has an effect in the two treatment groups.

You will take part in a study that is 28 weeks long, and at each visit you will be asked to do the following:

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

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Drink a small amount of "heavy water" (70-100 ml) to measure the amount of energy you burn on a daily basis. You will be asked to sit for 6 hours following the "heavy water" administration to make sure that you don't feel dizzy and to collect urine samples. During this 6-hour period, we will collect 3 urine samples from you (at hour 3, 4.5 and 6). After you have sat for 6 hours, it will be safe for you to leave the research center.
- Have your blood pressure and body weight /percent fat measured. Body weight will be measured by a digital scale, and percent fat will be measured by a handheld device.

Week 2 visit:

- Have urine collected
- You will also be asked to collect a stool sample so that the researchers can look at the types and amounts of bacteria in your gut. This will include genetic analysis of the bacteria in order to identify differences between them. You will be given a stool collection kit (including ice pack, zip lock bag, and instructions) to collect your stool sample, which you will bring to your follow up visit 1 week later.

Week 3 visit:

- Have urine collected

APPENDIX A - CONSENT FORM - (continued)

Week 4 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Have your energy level measured by wearing a small mask placed over your mouth/nose for 3 minutes
- Be given eating behavior and sleep habit questionnaires and a food record 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 your group assignment (time restricted feeding and calorie restriction groups only)
- You will also be given a stool collection kit (including ice pack, zip lock bag, and instructions) to collect your stool sample, which you will bring to your follow up visit 1 week later.

Week 5 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 6 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 7 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 8 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)
- Be given eating behavior and sleep habit questionnaires and a food record to fill out

Week 9 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 10 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 11 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 12 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)
- Be given eating behavior and sleep habit questionnaires and a food record to fill out

Week 13 visit:

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

APPENDIX A - CONSENT FORM - (continued)

- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 14 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 15 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 16 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Drink a small amount of "heavy water" (70-100 ml) to measure the amount of energy you burn on a daily basis. You will be asked to sit for 6 hours following the "heavy water" administration to make sure that you don't feel dizzy and to collect urine samples. During this 6-hour period, we will collect 3 urine samples from you (at hour 3, 4.5 and 6). After you have sat for 6 hours, it will be safe for you to leave the research center.
- Have your blood pressure and body weight /percent fat measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Have your energy level measured by wearing a small mask placed over your mouth/nose for 3 minutes
- Be given eating behavior and sleep habit questionnaires and a food record 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 your group assignment (time restricted feeding and calorie reduction groups only)
- You will also be given a stool collection kit (including ice pack, zip lock bag, and instructions) to collect your stool sample, which you will bring to your follow up visit 1 week later.

Week 17 visit:

- Have your blood pressure and body weight /percent fat measured
- Have urine collected
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 18 visit:

- Have your blood pressure and body weight /percent fat measured
- Have urine collected
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 19 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 20 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)
- Be given eating behavior and sleep habit questionnaires and a food record to fill out

Week 21 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

APPENDIX A - CONSENT FORM - (continued)

Week 22 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 23 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 24 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)
- Be given eating behavior and sleep habit questionnaires and a food record to fill out

Week 25 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 26 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)

Week 27 visit:

- Have your blood pressure and body weight /percent fat measured
- Be given dietary counseling (time restricted feeding and calorie reduction groups only)
- You will also be given a stool collection kit (including ice pack, zip lock bag, and instructions) to collect your stool sample, which you will bring to your follow up visit 1 week later.

Week 28 visit:

- Have a blood draw from a vein in your arm (about 4 teaspoons of blood)
- Have your blood pressure and body weight /percent fat measured
- Have a full-body x-ray to determine the distribution of fat in your body
- Have your energy level measured by wearing a small mask placed over your mouth/nose for 3 minutes
- Be given eating behavior and sleep habit questionnaires and a food record to fill out
- Be given an exercise monitor and instructed how and when to wear it
- Meet with the Dietician to learn how to maintain healthy eating habits once the study is over

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 160 ml of blood (approxiimately 32 teaspoons or 11 tablespoons) will be drawn during the study.
2. Time restricted feeding/reducing energy intake: Reducing daily energy intake has been shown to have beneficial effects on health. Studies of calorie reduction in people for 3 to 6 months have shown that it is generally well tolerated and has no harmful effects. You may feel hungry, however, which may be unpleasant.

APPENDIX A - CONSENT FORM - (continued)

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.

4. Heavy water administration: Heavy water (also called doubly labeled water) is a labeled form of water, which can be measured in trace amounts within your blood. It tastes and feels identical to water, contains no radioactivity, and has no known harmful effects at the doses given here. During the initial dosing it may cause some temporary dizziness in some people (about one out of every 30 people), although this is rare. In the rare event that dizziness occurs, this should go away within 1 hour, and will be treated symptomatically in the interim. Usually, lying down and resting for a brief period (an hour at most) is enough to allow the dizziness to go away. If dizziness happens more than once or persists, you will be removed from the study. Heavy water does not pose any risk to reproductive organs, including sperm or male fertility.

5. Confidentiality: Potential loss of confidentiality may also be a risk. Your personal information and results will be kept as confidential as possible. To maintain confidentiality, code numbers only will identify all lab specimens, and other records. 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.

6. Eating/sleep questionnaires: You may feel uncomfortable while answering the questions posed in the eating questionnaires. If this is the case, you can feel free to discuss this with the study coordinator, and you may choose to only answer the questions you feel confortable with.

7. Stool sample collection: You will be asked to collect a stool sample four times during this study. Collecting a stool sample involves placing a "hat", that will be provided by our staff, on your commode (toilet) before you are seated. This hat will collect the stool and then you can use a wooden stick and protective gloves, which will be provided by our staff, to transfer the stool sample into special zip lock bags. The special zip lock bags that contain the stool samples require refrigeration until you bring it into the study office during your regularly shcedule appoinment the next week. One of the special zip lock bags will have a fluid inside and you will be asked to press on the outside of the zip lock bag with your fingers to make sure the fluid is mixed with the stool sample you have provided. You may experience emotional stress related to working with your own stool. Mishandling stool can lead to infections. However, stool collection instructions will be reviewed with you and a safe hand washing technique will be taught to reduce risk of infection.

There is a Federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination if you have already been diagnosed with the genetic disease being tested.

There is a risk that someone could get access to the genetic information we have stored about you. Genetic testing can create information about a subjects' and their families' personal health risks and can cause or increase anxiety, and/or interfere with your ability to get insurance or a job, and can even lead to discrimination. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. There are laws against this kind of misuse, but they may not give full protection. There may be other unforeseen privacy risks. We believe the chance these things will happen is very small, but we cannot make guarantees. Your privacy and the confidentiality of your data

are very important to us and we will make every effort to protect them. These efforts are described in the section below called "What about privacy and confidentiality?".

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?

Based on experience with time restricted feeding or calorie reduction, researchers believe it may help people lose weight and lower heart disease risk. However, because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case. If you are assigned to no treatment, you are not expected to directly benefit from participating in this research

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 these 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.

APPENDIX A - CONSENT FORM - (continued)

Will health information about you be created, used or shared with others during this study?

State and federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect your health information. This section of this form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information in this research study. By signing this form you are authorizing [*add name of investigator or student/faculty*] [*add "and his/her research staff or team," if applicable*] to create, get, use, store, and share protected health information that identifies you for the purposes of this research.

The health information includes all information created and/or collected during the research as described within this consent form and/or any health information in your medical record that is needed for the research and that specifically includes the results of the blood, stool, DXA scan (body fat and muscle mass), height, weight, and questionnaires, that are part of the research that will become PHI, including personal identifiers such as name, telephone number, demographic information, e.g. age, race, gender and date of birth.

During the conduct of the research, the researchers may use or share your health information:

- With each other and with other researchers involved with the study;

How will your health information be protected?

The researchers agree to protect your health information and will only share this information as described within this research consent/authorization form. When your health information is given to people outside of the research study, those agencies that receive your health information may not be required by federal privacy laws (such as the Privacy Rule) to protect it. They may also share your information with others without your permission, if permitted by laws that they have to follow.

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?

There are no costs to you for participating in this research.

APPENDIX A - CONSENT FORM - (continued)

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.

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. For your safety, however, you should consider the investigator's advice about how to leave the study. If you leave the study before the final planned study visit, the investigator may ask you to complete the final steps.

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.

Your Authorization for release of health information for this research study expires at the end of the study, but can be canceled sooner if you decide to withdraw your permission. You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to: Krista Varady, PhD, University of Illinois at Chicago, Department of Kinesiology and Nutrition, 1919 West Taylor Street, Room 532, Chicago, IL, 60612. If you cancel this Authorization, you may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information they have already obtained as necessary to maintain the integrity and reliability of the research and to report any adverse (bad) effects that may have happened to you.

Who should I contact if I have questions?

Contact the researchers Dr. Krista Varady (312-996-7897) or Kristin Hoddy (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.

If you have questions or concerns regarding your privacy rights under HIPAA, you should contact the University of Illinois at Chicago Privacy Officer at Ph: (312) 996-2271.

Right to Refuse to Sign this Authorization: You do not have to sign this Consent/Authorization. However, because your health information is required for research participation, you cannot be in this research study if you do not sign this form. If you decide not to sign this Consent/Authorization form, it will only mean you cannot take part in this research. Not signing this form will not affect your non-research related treatment, payment or enrollment in any health plans or your eligibility for other medical benefits.

APPENDIX A - CONSENT FORM - (continued)

What if I am a UIC student?

You may choose not to participate or to stop your participation in this research at any time. This will not affect your class standing or grades at UIC. The investigator may also end your participation in the research. If this happens, your class standing or grades will not be affected. You will not be offered or receive any special consideration if you participate in this research.

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 or Legally Authorized Representative

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.

If you have not already received a copy of the Notice of Privacy Practices, you should ask for one. Your signature below indicates that you are providing both consent to participate in the research study and authorization for the researcher to use and share your health information for the research.

_____ _____

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

Volunteers needed for a

Weight Loss Study

Volunteers are needed for a 28-week research study of the effects of a time restricted feeding diet for weight loss and heart disease prevention.

The study is open to men and women who are:

Between the ages of 25 and 65 •

Obese, not diabetic, sedentary or moderately active •

For more information, please call: 312-355-0542

Kristin Hoddy
Weight loss study
312-355-0542

Kristin Hoddy
Weight loss study
312-355-0542

Kristin Hoddy
Weight loss study
312-355-0542

Kristin Hoddy
Weight loss study
312-355-0542

Kristin Hoddy
Weight loss study
312-355-0542

University of Illinois at Chicago
Department of Kinesiology and Nutrition
1919 West Taylor Street, Chicago, IL
Krista Varady, Ph.D., Principal Investigator

UIC

Time restricted feeding for weight loss
Version 3, March 29 2016

APPENDIX C – SCREENING QUESTIONNAIRE

Screening questionnaire

Subject ID: 017 –

Date of screening: _____

First name: _____ Middle initial: ____ Last: _____

Phone: _____ Email: _____

Age: _____ (Must be 25-65 yrs) DOB: _____ Sex: ☐ Female ☐ Male

Weight: _____ Height: _____ BMI: _____ (must be 30-45kg/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 14 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 heart disease or stroke, history of eating disorders/binge eating)

Are you on any medications? ☐ yes ☐ no

Medication 1: _____

Medication 2: _____

Medication 3: _____

(Must not be taking weight loss medications)

Taking calcium or vitamin D supplement? Dose/day: _____

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)

APPENDIX D - TIME - RESTRCTED FEEDING INSTRUCTIONS

Time Restricted Feeding (TRF) diet guidelines

WHEN can I eat each day?

- Start eating at 10am each day (do not consume food before this time)
- Stop eating at 6pm 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 (10am to 6pm)
- 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 at the weekly sessions
- 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 (this will be discussed in detail during the session on alcohol)

What can I consume during the non-eating period? (6pm to 10am)

- 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 dietary counseling sessions)
- Occasionally, the dietician will ask you to complete a 3-day food record to monitor your eating habits
- Please bring these forms with you to each counseling session

APPENDIX E - FOOD RECORD

Food Record – Day 1 ☐ **Feed day** ☐ **Fast day**

Subject ID: _____ Date: _____ Study week: _____

Time	Food Description	Amount

APPENDIX F - BODY SHAPE QUESTIONAIRE

Body Shape Questionnaire (BSQ)

We would like to know how you have been feeling about your appearance over the past two weeks.
Please read each question and circle the appropriate number. Please answer all the questions.

	Never	Rarely	Sometimes	Often	Very often	Always
1. Have you been so worried about your shape that you have been feeling that you ought to diet?	1	2	3	4	5	6
2. Has being with thin people made you feel self-conscious about your shape?	1	2	3	4	5	6
3. Have you ever noticed the shape of other people and felt that your own shape compared unfavourably?	1	2	3	4	5	6
4. Has being undressed, such as when taking a bath, made you feel fat?	1	2	3	4	5	6
5. Has eating sweets, cakes or other high calorie food made you feel fat?	1	2	3	4	5	6
6. Have you felt excessively large and rounded?	1	2	3	4	5	6
7. Have you felt ashamed of your body?	1	2	3	4	5	6
8. Has worry about your shape made you diet?	1	2	3	4	5	6

APPENDIX F - BODY SHAPE QUESTIONAIRE (continued)

Body Shape Questionnaire (BSQ) – Continued

	Never	Rarely	Sometimes	Often	Very often	Always
9. Have you thought that you are the shape you are because you lack self-control?	1	2	3	4	5	6
10. Have you worried about other people seeing rolls of fat around your waist and stomach?	1	2	3	4	5	6
11. Have you felt that it is not fair that other people are thinner than you?	1	2	3	4	5	6
12. Has seeing your reflection in a mirror or shop window made you feel bad about your shape?	1	2	3	4	5	6
13. Have you been particularly self-conscious about your shape when in the company of other people?	1	2	3	4	5	6
14. Has worry about your shape made you feel you ought to exercise?	1	2	3	4	5	6

APPENDIX G- MULTIDIMINSIONAL ASSESSMENT OF EATING DISORDER SYMPTOMS (MEADS)

MAEDS

Name: _____ Date: _____

Instructions: Using the scale below, please rate the following items on a scale from 1 to 7. Please answer as truthfully as possible.

1 = Never
2 = Very Rarely
3 = Rarely
4 = Sometimes
5 = Often
6 = Very Often
7 = Always

APPENDIX G – MULTIDIMINSIONAL ASSESSMENT OF EATING DISORDER SYMPTOMS (MAEDS) (continued)

1----------2----------3----------4----------5----------6----------7
NEVER VERY RARELY RARELY SOMETIMES OFTEN VERY OFTEN ALWAYS

1. Fasting is a good way to lose weight.
1 2 3 4 5 6 7

2. My sleep isn't as good as it used to be.
1 2 3 4 5 6 7

3. I avoid eating for as long as I can.
1 2 3 4 5 6 7

4. Certain foods are "forbidden" for me to eat.
1 2 3 4 5 6 7

5. I can't keep certain foods in my house because I will binge on them.
1 2 3 4 5 6 7

6. I can easily make myself vomit.
1 2 3 4 5 6 7

7. I feel that being fat is terrible.
1 2 3 4 5 6 7

8. I avoid greasy foods.
1 2 3 4 5 6 7

9. It's okay to binge and purge once in a while.
1 2 3 4 5 6 7

10. I don't eat certain foods.
1 2 3 4 5 6 7

11. I think I am a good person.
1 2 3 4 5 6 7

12. My eating is normal.
1 2 3 4 5 6 7

13. I can't seen to concentrate lately.
1 2 3 4 5 6 7

14. I try to diet by fasting.
1 2 3 4 5 6 7

APPENDIX G – MULTIDIMINSIONAL ASSESSMENT OF EATING DISORDER SYMPTOMS (MAEDS) (continued)

1----------2----------3----------4----------5----------6----------7
NEVER VERY RARELY RARELY SOMETIMES OFTEN VERY OFTEN ALWAYS

15. I vomit to control my weight.
1 2 3 4 5 6 7

16. Lately nothing seems enjoyable anymore.
1 2 3 4 5 6 7

17. Laxatives help keep you slim.
1 2 3 4 5 6 7

18. I don't eat red meat.
1 2 3 4 5 6 7

19. I eat so rapidly I can't even taste my food.
1 2 3 4 5 6 7

20. I do everything I can to avoid being overweight.
1 2 3 4 5 6 7

21. When I feel bloated, I must do something to rid myself of that feeling.
1 2 3 4 5 6 7

22. I overeat too frequently.
1 2 3 4 5 6 7

23. It's okay to be overweight.
1 2 3 4 5 6 7

24. Recently I have felt that I am a worthless person.
1 2 3 4 5 6 7

25. I would be very upset if I gained 2 pounds.
1 2 3 4 5 6 7

26. I crave sweets and carbohydrates.
1 2 3 4 5 6 7

27. I lose control when I eat.
1 2 3 4 5 6 7

28. Being fat would be terrible
1 2 3 4 5 6 7

APPENDIX G - MULTIDIMINSIONAL ASSESSMENT OF EATING DISORDER SYMPTOMS (MAEDS) (continued)

1----------2----------3----------4----------5----------6----------7
NEVER VERY RARELY RARELY SOMETIMES OFTEN VERY OFTEN ALWAYS

29. I have thought seriously about suicide lately.
1 2 3 4 5 6 7

30. I don't have any energy anymore.
1 2 3 4 5 6 7

31. I eat small portions to control my weight.
1 2 3 4 5 6 7

32. I eat 3 meals a day.
1 2 3 4 5 6 7

33. Lately I have been easily irritated.
1 2 3 4 5 6 7

34. Some foods should be totally avoided.
1 2 3 4 5 6 7

35. I use laxatives to control my weight.
1 2 3 4 5 6 7

36. I am terrified by the thought of being overweight.
1 2 3 4 5 6 7

37. Purging is a good way to lose weight.
1 2 3 4 5 6 7

38. I avoid fatty foods.
1 2 3 4 5 6 7

39. Recently I have felt pretty blue.
1 2 3 4 5 6 7

40. I am obsessed with becoming overweight.
1 2 3 4 5 6 7

41. I don't eat fried foods.
1 2 3 4 5 6 7

42. I skip meals.
1 2 3 4 5 6 7

APPENDIX G – MULTIDIMINSIONAL ASSESSMENT OF EATING DISORDER SYMPTOMS (MAEDS) (continued)

1----------2----------3----------4----------5----------6----------7
NEVER VERY RARELY RARELY SOMETIMES OFTEN VERY OFTEN ALWAYS

43. Fat people are unhappy.
1 2 3 4 5 6 7

44. People are too concerned with the way I eat.
1 2 3 4 5 6 7

45. I feel good when I skip meals.
1 2 3 4 5 6 7

46. I avoid foods with sugar.
1 2 3 4 5 6 7

47. I hate it when I feel fat.
1 2 3 4 5 6 7

48. I am too fat.
1 2 3 4 5 6 7

49. I eat until I am completely stuffed.
1 2 3 4 5 6 7

50. I hate to eat.
1 2 3 4 5 6 7

51. I feel guilty about a lot of things these days.
1 2 3 4 5 6 7

52. I'm very careful of what I eat.
1 2 3 4 5 6 7

53. I can "hold off" and not eat even if I am hungry.
1 2 3 4 5 6 7

54. I eat even when I am not hungry.
1 2 3 4 5 6 7

55. Fat people are disgusting.
1 2 3 4 5 6 7

56. I wouldn't mind gaining a few pounds.
1 2 3 4 5 6 7

APPENDIX H - INSOMNIA SEVERITY INDEX (ISI)

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 - BERLIN 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 - 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 K - 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		

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XI. VITA: Kelsey Gabel, MS, RD, LDN

Education

PhD Human Nutrition	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2016 – Present Thesis: Effect of time-restricted feeding on body weight and metabolic disease risk Supervisor: Dr. Krista Varady, Ph.D.
MS Human Nutrition	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2013 – December 2015
B.S. Music Education	**Kansas State University – School of Music, Theatre, and Dance** August 2003 – May 2006

Research Appointments

Clinical Coordinator	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2016 – Current
Clinical Coordinator	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2014 – December 2016
Lab technician	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2014 – December 2016

Teaching Appointments

Lecturer	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2016-Present Nutrition Science II (Undergraduate level), Nutrition Assessment (Undergraduate level)
Teaching Assistant	**University of Illinois at Chicago – Department of Kinesiology and Nutrition** August 2016 – Present Nutrition Assessment, Nutrition Science 2 (Undergraduate level) Obesity, Advanced Public Health Nutrition, Special topics in Human Nutrition (Graduate level)

Professional Positions

Dietitian/Owner	**Whole Food Fueling** - Private Practice 2016-Present
Coach	**Coalition Strength and Conditioning** 2010-Present
Internship Rotation	**2014-2015 University of Illinois at Chicago MS/CP**

Heartland Health Alliance – Vital Bridges
Specializes in optimizing nutrition and food availability for those with the HIV+/AIDS virus whom are part of Chicago's most vulnerable populations
Mercy Hospital
Clinical nutrition rotation including general medical floor, cardiac floor, ICU, NICU, and in-patient Diabetes. Independently ran NICU nutrition for 6 weeks. Proficient with Cerner software.
Mariano's Fresh Market
Corporate wellness cooking event, grocery store tours, healthy substitutions to fast food youth program
University of Illinois at Chicago Dining Center East
Gluten Free Menu Analysis and creation of a 600 Calorie Menu
Advocate Sykes Medical Center
Diabetes outpatient nutrition education. Specialized in weight loss and gestational diabetes management and education. Proficient with AllScripts software

Honors and Awards

2018	Kamath Award - University of Illinois, Chicago
2014	Board of Trustees Tuition Award - University of Illinois, Chicago
2014	GCSAA Legacy Award – Golf course Superintendents Association of America and Syngenta
2014	Van Doren Scholarship – University of Illinois Foundation
2013	KGCSA Legacy Award – Kansas golf course Superintendents Association
2001	Friends University – Presidential Scholarship

Licenses and Certificates

2016-Present	ACEND Registered Dietitian Nutritionist
2011-Present	Crossfit Level 1 &2 Coach
2012-Present	Crossfit Endurance Coach
2015-Present	Precision Nutrition Level 1 Coach

Professional Affiliations

Member of the Academy of Nutrition and Dietetics since 2013

- Dietitians in Integrative and Functional Medicine DPG
- Sports, Cardiovascular, and Wellness Nutrition DPG

Member of the Obesity Society since 2016
Member of the American Society for Nutrition since 2016

Research Funding

COMPLETED

Campus Research Board Varady, K (PI) 7/1/16-6/30/17
University of Illinois at Chicago
Time restricted feeding for weight loss
This study compares the effects of time restricted feeding versus daily calorie restriction on body weight, body composition, and coronary heart disease risk factors in obese sedentary adults.
Role: Co-I

R01 HL106228, NIH (NHLBI) Varady (PI) 6/1/11 – 1/31/16
Alternate day fasting for weight loss, weight maintenance, and cardio-protection
The goal of this study was to compare the effects of alternate day fasting versus calorie restriction on body weight, body composition, and coronary heart disease risk factors during 6 months of weight loss followed by 6 months of weight maintenance in obese humans.
Role: Clinical Coordinator

Publications

1. **Gabel K**, Kroeger CM, Trepanowski JF, Cienfuegos S, Kalam F, Varady KA. Differential effects of alternate day fasting versus daily calorie restriction on insulin resistance: A secondary analysis of a 12-month randomized controlled trial. 2019. Obesity: Accepted.

2. **Gabel K**, Hoddy KK, Burgess HJ, Varady KA. Effect of 8-hour time-restricted feeding on sleep quality and duration in adults with obesity. Applied Physiology, Nutrition, and Metabolism: e-pub: 2019 Feb 25.

3. 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. Nutrition and Health, 2019: Accepted.

4. **Gabel K**, Hoddy KK, Varady KA. Safety of 8-hour time-restricted feeding in subjects with obesity. Applied Physiology, Nutrition, and Metabolism, 2019, 44(1): 107-109.

5. **Gabel K**, Hoddy KK, Haggerty N, Song J, Kroeger CA, Trepanowski JF, Panda S, Varady KA. Effect 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: 345-353.

6. Barnosky A, Kroeger CM, Trepanowski JF, Klempel MC, Bhutani S, Hoddy KK, **Gabel K**, Shapses SA, Varady KA. Effect of alternate day fasting on markers of bone metabolism: An exploratory analysis of a 6-month randomized controlled trial. Nutr Healthy Aging. 2017;4(3):255-263.

7. Hoddy KK, Gibbons C, Kroeger CM, Trepanposki JF, Barnosky A, Bhutani S, **Gabel K**, Finlayson G, Varady KA. Changes in hunger and fullness in relation to gut peptides before and after 8 weeks of alternate day fasting. Clin Nutr. 2016;35(6):1380-1385.

8. Kroeger CM, Trepanowski JF, Klempel MC, Barnosky A, Bhutani S, **Gabel K**, Varady KA. Eating behavior traits of successful weight losers during 12 months of alternate-day fasting: An exploratory analysis of a

randomized controlled trial. Nutr Health. 2018:260106017753487.

9. Trepanowski JF, Kroeger CM, Barnosky AR, Klempel MC, Bhutani S, Hoddy KK, **Gabel K**, Freels S, Rigdon J, Rood J, Ravussin E, Varady KA. Alternate day fasting for weight loss and weight maintenance: A randomized controlled trial. JAMA. 201: 2017;177(7):930-938.

Abstracts

1. **Gabel K**, Varady KA. Effect of 12 weeks of 8-h time restricted feeding on sleep quality and quantity in subjects with obesity. The Obesity Week, Nashville, TN, 2018 [Poster Presentation]

2. **Gabel K**, Varady KA, Health benefits of time restricted feeding. Diabetes and Obesity Research Day, Chicago, IL 2018. [Presentation]

3. **Gabel K**, Varady KA. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in adults with obesity. Nutrition, Boston, MA, 2018. [presentation]

4. **Gabel K,** Varady KA. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in adults with obesity. UIC Student Research Forum, 2018. [Poster presentation]

5. **Gabel K**, Hoddy KK, Haggerty N, Varady KA. Effect of 8-Hour Time Restricted Feeding on Body Weight in Obese Subjects. Diabetes and Obesity Research Day, Chicago, IL, 2017. [Poster presentation]

6. **Gabel K**, Hoddy KK, Haggerty N, Varady KA. Effect of 8-Hour Time Restricted Feeding on Body Weight in Obese Subjects. Experimental Biology, Chicago, IL, 2017. [Poster presentation]

Invited Talks

1. **Gabel K**, Varady KA, Health benefits of time restricted feeding. Diabetes and Obesity Research Day, Chicago, IL 2018. [Presentation]

Post-doc Interviews

T-32 Fellowship University of Alabama Birmingham - NORC, DRC, USDC
February 2019

T-32 Fellowship University of Illinois at Chicago - PREMIER
February 2019

Graduate Student Supervision

Jeehee Song, Chiajun Lim, Nicole Haggerty 2016-2017
Faiza Kalam, Sofia Cienfuegos 2017-present

Professional Service

Journal Review
Journal of Human Nutrition and Dietetics, Nutrition Reviews, International Journal of Obesity

Media Attention

Endocrine Today	Time restricted feeding shows promising sleep results in study	2018
Wall Street Journal	A diet strategy that counts time, not calories	2018
Today.com	Four tips to keep an intermittent fasting diet on track	2018
Today.com	Intermittent fasting made easy: What to know about the 16:8 diet	2018