Meal-time Matters: An 8-week Randomized Control Trial to Examine the Effects of a Daily 18-hour Fast on Diet Quality in College Students

by

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ABSTRACT

Background. College students' modifiable health behaviors, including unhealthful eating patterns, predispose them to risk for future cardiometabolic conditions.

Purpose. This novel 8-week randomized control parallel-arm study compared the effects of a daily 18-hour Time-Restricted Feeding protocol vs. an 8-hour fast on diet quality in college students. Secondary outcomes were resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures.

Methods. Eighteen healthy college students (age = 23 ± 4 years; BMI = 23.2 ± 2.3 kg/m2; MET = 58.8 ± 32.9 min/wk) completed this study. Participants were randomized to a daily 18-hour fasting protocol (Intervention; n = 8) or a daily 8-hour fasting protocol (Control; n = 10) for eight weeks. One 'cheat' day was permitted each week. Outcomes were measured at weeks 0 (baseline), 4, and 8. A non-parametric Mann Whitney U test was used to compare the week 4 change from baseline between groups. Statistical significance was set at $p \leq 0.05$.

Results. Diet quality ($p = 0.030$) and body weight ($p = 0.016$) improved from baseline to week 4 for the INV group in comparison to the CON group. The data suggest these improvements may be related to reductions in snacking frequency and increased breakfast consumption. Fasting blood glucose and hip circumference tended to improve for the INV group in comparison to the CON group ($p = 0.091$ and $p = 0.100$). However, saturated fat intake tended to increase in the INV group in comparison to the CON group ($p = 0.064$). Finally, there were no treatment differences between groups ($p>0.05$) for the 4-week change in total calories, dietary vitamin C, added sugars, resting systolic blood

pressure, resting diastolic blood pressure, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, waist circumference, or MET.

Conclusion. These data, although preliminary, suggest that the 18-hour fasting protocol was effective for improving diet quality and reducing weight in comparison to the 8-hour fasting protocol in healthy college students. Future intervention trials will need to confirm these findings and determine the long-term relevance of these improvements for health outcomes.

DEDICATION

I dedicate this project to my beautiful mom. Thank you for your love, support, and continued demonstration of hard work, selflessness, and resiliency.

To my darling – while no words can truly capture how much you mean to me, I love you dearly and continue to be motivated by your kindness and humility. In the words of Michael Scott, *"you are of the highest kind, quality, and order. Supreme."*

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CHAPTER 1
INTRODUCTION

Problem

College students' modifiable health behaviors predispose them to future chronic health conditions, including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Research points to prolonged unhealthful lifestyle practices such as night-time ingestion and inadequate fruit and vegetable (F&V) intake as contributors to the problem.[1,2] Public surveys of nationally representative samples (total n >50,000) revealed that 11-13% of respondents consumed 50% of their daily calories after 7 PM.[3] Additionally, 9% - 12% of participants ate after 11 PM. Interestingly, the prevalence of night eating is highest among adults 18-30 years old, highlighting young adulthood as a period where night eating is of particular concern as the meals and snacks consumed at night are typically energy-dense with little added nutritional value.[3,4] Along with night eating, findings from the 2018 National College Health Assessment, a nationally recognized survey conducted to examine students' health habits, found that among undergraduates (n = 19,664; 40 post-secondary institutions), 96% of students failed to meet the national recommendations for F&V intake.[5]

Considering that poor eating habits are associated with weight gain[6,7] it is not surprising that one in three undergraduate students are overweight or obese.[5] Additionally, survey data collected from over 16,000 college students in post-secondary education institutions in Minnesota revealed even higher prevalence rates for overweight and obesity: 37% and 46% for 4-year and 2-y institutions, respectively.[8] Interestingly, the rate of weight gain in college students is faster, and in some cases, fivefold times that of

the general population.[9,10] Furthermore, while the majority of weight gain is experienced during the freshman year, weight gain typically persists throughout college and into adulthood, increasing the likelihood of chronic health conditions over time.[11,12] Additionally, it has been reported that weight gain in college is rapid and can range between 1.5 – 6.8 lbs. in the first two semesters[13] with much of that weight occurring within the first several months of college.[13,14] Indeed, among a sample of freshmen (n = 1095), weight gain averaged 2.4 lbs. within the first three months of college.[14]

Given the strong and persistent relationship between obesity and an increased risk for chronic conditions including CVD and T2DM,[15–17] not to mention the exorbitant healthcare costs associated with these conditions,[18,19] it is crucial to establish achievable and sustainable interventions to improve health at the collegiate level. In response to calls such as those from the Surgeon General's Vision for a Healthy and Fit Nation to improve health on college campuses, a number of studies have been conducted to improve college students' health. Overall, these undertakings have shown some promise and have also demonstrated that college students are receptive to health initiatives.[20] However, college students continue to struggle with their eating patterns and their overall health.[5] Indeed, among a sample of students attending a Midwestern university (n = 462), 33% of participants have at least one metabolic abnormality while 6% had two or more.[21] Additionally, 22% and 12.6% of students had high waist circumference and elevated serum triglycerides, respectively.

An emerging line of inquiry into time-restricted feeding (TRF), a form of intermittent fasting (IF), may offer a cost-effective opportunity to improve diet quality and cardiometabolic health in college students as TRF extends the nightly fast and allows

ad libitum consumption of energy-containing foods and beverages within a pre-defined eating window.[22] Preliminary exploration of TRF has yielded favorable findings. Specifically, Stote demonstrated that an 8-week TRF protocol resulted in improvements in HDL cholesterol in middle-aged adults (n = 15).[23] Next, Gabel and colleagues reported that adults with obesity (n = 23) adhering to a 12-week TRF protocol had a 2.6% reduction in body weight and a 7 mm Hg reduction in systolic blood pressure, [24] while LeCheminant and colleagues reported an average weight loss of one pound following a 2-week TRF protocol in normal-weight men (n = 29).[25]

Additionally, an investigation by Moro et al. demonstrated that an 8-week TRF protocol effectively reduced triglycerides, fasting insulin, fasting glucose, and HOMA-IR in men (n = 34).[26] Next, Sutton et al. reported a reduction in systolic blood pressure, diastolic blood pressure, and fasting insulin in a sample of men (n = 8) following a 10-week crossover study with an 18-hour TRF protocol.[27] Additionally, Gill and Panda reported a mean reduction in daily caloric intake by 20.26%, and a 3.27 kg weight loss for participants adhering to a 12-14 hour TRF protocol for 16 weeks (n = 8).[28] The authors contend that the decrease in daily caloric intake occurred as a result of reducing the eating duration. Interestingly, the authors reported that participants ate in a "time-of-the-day-dependent manner," where certain foods and beverages typically consumed at specific times (e.g., coffee in the mornings) were eliminated from their diet during the intervention phase due to the reduced eating duration. Finally, by utilizing a 4-week randomized, parallel-arm study design, Johnston and colleagues reported significant improvements in BMI and anger in participants randomized to a TRF group vs. a control group (n = 5 and n = 6, respectively).[29]

Collectively, these studies suggest that TRF may offer health benefits in a variety of study populations and highlight college students' receptiveness to TRF interventions. However, no known studies have assessed the effects of TRF on diet quality. Given college students' current eating patterns and partiality for night-time ingestion, this study presents an exciting opportunity to examine the effects of a cost-effective and adaptable TRF protocol to improve diet quality at the collegiate level. Thus, findings from the proposed undertaking may be used to design appropriate lifestyle interventions to improve diet quality in otherwise healthy college students.

Purpose of the Study

The primary outcome of this 8-week randomized parallel-arm study was to examine the effects of a daily 18-hour TRF protocol vs. an 8-hour TRF protocol on diet quality. Diet quality was measured by the Rapid Eating Assessment for Participants [shortened version] REAP-S questionnaire. Secondary outcomes were resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures and physical activity. The study was conducted with students enrolled at Arizona State University (ASU), and participants were randomized to either the intervention (INV) group (i.e., 18-hour fast) or the control (CON) group (i.e., 8-hour fast). Both groups were instructed to adhere to their customary eating patterns and exercise habits for the duration of the study.

Research Aims and Hypotheses

Primary Study Aim: To evaluate the effects of a daily 18-hour TRF protocol, completed daily for eight weeks, on diet quality with healthy ASU students.

Secondary Study Aims: To evaluate the effects of a daily 18-hour TRF protocol, completed daily for eight weeks, on resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures and physical activity with healthy ASU students.

Primary Research Question: What are the effects of a daily 18-hour fast vs. a daily 8-hour fast on diet quality in healthy college students?

> **H_a**: A daily 18-hour fast vs. a daily 8-hour fast will improve diet quality in healthy college students.

Secondary Research Question 1: What are the effects of a daily 18-hour fast vs. a daily 8-hour fast on fasting resting morning blood pressure in healthy college students?

> **H_a:** A daily 18-hour fast vs. a daily 8-hour fast will improve resting morning blood pressure in healthy college students.

Secondary Research Question 2: What are the effects of a daily 18-hour fast vs. a daily 8-hour fast on biomarkers of glucose regulation (i.e., fasting glucose and insulin) in healthy college students?

> **H_a:** A daily 18-hour fast vs. a daily 8-hour fast will improve biomarkers of glucose regulation (i.e., fasting glucose and insulin) in healthy college students.

***Secondary Research Question 3*:** What are the effects of a daily 18-hour fast vs. a daily 8-hour fast on biomarkers of lipid metabolism (i.e., LDL cholesterol, triglycerides, and HDL cholesterol) in healthy college students?

> **H_a:** A daily 18-hour fast vs. a daily 8-hour fast will improve biomarkers of lipid metabolism (i.e., LDL cholesterol, triglycerides, and HDL cholesterol) in healthy college students.

Secondary Research Question 4: What are the effects of a daily 18-hour fast vs. a daily 8-hour fast on anthropometric measures (i.e., body weight, waist circumference, and hip circumference) in healthy college students?

> **H_a**: A daily 18-hour fast vs. a daily 8-hour fast will improve anthropometric measures (i.e., body weight, waist circumference, and hip circumference) in healthy college students.

Definition of Terms

Intermittent fasting: a hypernym for fasting protocols believed to favorably impact health.[22]

Time-restricted feeding: a protocol that requires individuals to consume energy-containing foods and beverages within specific eating windows.[22]

Eating pattern: a representation of all foods and beverages consumed on a regular basis.

Cardiovascular disease: pathological conditions that affect the heart or blood vessels.

Low-density lipoprotein (LDL): a type of lipoprotein that carries cholesterol to the cells. Excess LDL (known as "bad" cholesterol) contributes to atherosclerosis, which may increase the risk for strokes and heart attacks.[30]

High-density lipoprotein (HDL): a type of lipoprotein that carries LDL cholesterol away from the arteries and into the liver for breakdown. High HDL (known as "good" cholesterol) may be protective against strokes and heart attacks.[30]

Triglycerides (TG): a type of fat that, when combined with excess LDL and low HDL, may contribute to atherosclerosis and increase the risk for strokes and heart attacks.[30]

Type 2 diabetes mellitus: a chronic health condition characterized by the body's inability to use insulin properly. The result is high levels of glucose in the blood which increases the likelihood for nerve damage, kidney disease, and strokes.[31]

Delimitations and Limitations

The study was delimited to recreationally active (<450 minutes of activity/week; not training or competing for an event) college students (18-29 years old) with normal to overweight BMI classification (18.5-29.9 kg/m^2). Participants were healthy by self-report and free of acute illness or diagnosed chronic disease. Prescription medication was allowed if the use had been in place for >3 months and was continued throughout the study. Participants were not excluded based on race/ethnicity or socioeconomic status. Findings from this research may not extend beyond the population of interest.

Due to COVID-19 restrictions, several participants were unable to visit the research laboratory to obtain anthropometric measurements and blood data at week 8. As a result of these restrictions, week 8 data were not as robust as originally planned. Therefore, reliance was placed on the Mann-Whitney U test for statistical analyses, and the change in outcomes from baseline to week 4 were used to test the hypotheses. Finally, participants enrolled in the present study were predominantly healthy, which may partially explain why select outcome measures showed no significant improvements. As such, it may be prudent for future studies to recruit participants at greater risk for cardiometabolic conditions.

CHAPTER 2
REVIEW OF LITERATURE

Overview

Diet quality is a measure of how well eating patterns align with nutrition guidelines.[32] National dietary surveillance data indicate that over 90% of Americans (≥ 2 years old) do not meet federal recommendations for healthful eating. Similar observations have been made in college students. Indeed, the most recent national collegiate dietary data (n = 67,405), ACHA Spring 2019, revealed that almost 96% of college students fail to meet federal recommendations for fruit and vegetable intake.[33] Conversely, calorically dense convenience foods, including those high in added sugar, fat, and sodium, appear to be preferential for young adults. These data indicate that the typical American diet is one of lower diet quality and that these findings extend to the college population.

Globally, it is well known that chronic, non-communicable diseases, including conditions affecting the cardiovascular system (CVD) and type 2 diabetes mellitus (T2DM) and are among the leading causes of morbidity and mortality. Indeed, in the United States (U.S.), ischemic heart disease, stroke, and T2DM are major contributors to the nation's 3.3 trillion-dollar annual healthcare cost.[34,35] The Centers for Disease Control and Prevention (CDC) has operationalized chronic diseases as ongoing (≥ one year) conditions that interfere with activities of daily living require medical attention, and/or pharmacologic intercession.[35] Nationally, it is estimated that six in ten adults are diagnosed with one chronic disease while four in ten adults have two or more of these conditions.[36]

It is well established that chronic diseases have complex etiologies that include both modifiable and non-modifiable factors. Low diet quality, physical inactivity, excess alcohol consumption, and smoking are among the most important modifiable factors that can increase chronic disease risk and negatively impact overall health.[35] Further, obesity and the presence of cardiometabolic perturbations associated with metabolic syndrome (MetS) have been shown to hasten chronic disease prognosis. Considering the cost and health advantages of targeting modifiable lifestyle factors, not to mention the deleterious effects of prolonged unhealthful eating patterns, it is vital to explore the role of interventions focused on diet quality to avert or delay chronic disease onset. Thus, the intent of this review of literature is to 1) discuss how diet quality relates to health and disease, 2) highlight indices used to assess diet quality, 3) examine the relationship between diet quality, disease etiology, and mortality, 4) discuss eating patterns of college students, 5) examine the history of fasting, 6) highlight potential mechanisms associated with intermittent fasting, and 7) examine the efficacy of intermittent fasting to improve health conditions including diabetes, hypertension, obesity, and metabolic syndrome.

1. Health, Eating Patterns, and Diet Quality

The interest in health predates modern scientific advancements and notable medical discoveries. Indeed, early Hippocratic philosophy emphasized health promotion among the main categories of care whereby nutrition and physical activity were deemed essential to physical and mental health.[37] Currently, the emphasis on health promotion, disease prevention, and amelioration are at the forefront of many public health and research initiatives.[38] For instance, every five years, the United States Department of Health and Human Services and the United States Department of Agriculture publishes

the Dietary Guidelines for Americans (DGA), a comprehensive resource designed to help Americans adopt a more healthful, high quality diet. Recommendations provided by the DGA are based on current scientific literature and medical knowledge, and much of the guidance provided by the DGA emphasizes the role of foods, including F&V and whole grains, to delay disease onset. Along with the DGA, the World Health Organization defines a healthful diet as an eating pattern that promotes health, protects against chronic diseases, or reduces symptoms associated with chronic health conditions.[39] Currently, the scientific literature is burgeoning with research highlighting the importance of adopting and maintaining a healthful diet and has highlighted a spectrum of foods that should be included as part of a healthful eating pattern.[40–43]

***Fruits and Vegetables*.** F&V are regarded as nutrition powerhouses as they supply energy, dietary fiber, vitamins, minerals, and phytochemicals. Further, fruit and vegetable consumption is consistently linked to a reduced risk for chronic diseases.[44–46] In particular, adequate fruit and vegetable consumption has been shown to reduce the risk for T2DM and CVDs.[45,47–50] In their meta-analysis of prospective cohort studies, Li et al. reported that, among participants (n = 434, 342; aged: 24-79 years), higher consumption of leafy green vegetables and fruits was associated with a significantly reduced risk for T2DM.[50] Specifically, an increase of one serving of fruits per day was associated with 6% reduction in risk for T2DM (RR = 0.93). Similarly, one serving of vegetables per day was associated with a reduction in risk for T2DM (RR = 0.93). Interestingly, just 0.2 servings of leafy green vegetables resulted in a greater reduction (by 13%) in risk of T2DM (RR = 0.87) compared to general intake fruit or vegetable. Importantly, experimental trials examining the effects of dietary changes have also yielded favorable

outcomes. Specifically, data from the Diabetes Community Lifestyle Improvement Program found that the one-year incidence of T2DM was reduced by 50%.

Further, the authors reported a mean of 185.6 fewer calories per day and an increase of 33.4 g per 1000 kcal of F&V per day. The 6-month randomized control trial study was conducted on prediabetic Asian Indian adults with overweight or obesity (n = 283 CON; n = 295 INV), and consisted of a physician's visit, a meeting with a dietitian, and weekly classes focused on healthful dietary changes and weight loss strategies (Ford 2019).[51] Additionally, Ford and colleagues conducted a randomized controlled trial to examine the effects of a bilberry-rich diet on serum hippuric acid in adults with select criteria of MetS (n = 47) demonstrated a significant improvement in fasting hippuric acid following the consumption of the anthocyanin-rich diet.[52] Levels of hippuric acid have been proposed as a biomarker of polyphenol consumption, and the authors reported that changes in serum hippuric acid were inversely correlated with changes in fasting plasma glucose after adjustment for BMI.

Epidemiologic data show inverse associations between consumption of F&V (e.g., citrus, cruciferous vegetables, apples, and pears) and CVD and mortality.[53] According to results from the European Prospective Investigation into Cancer and Nutrition (EPIC) Heart Study, participants (n = 313, 074; mean age = 54 years; average follow-up = 8.4 years) had a 4% lower risk for ischemic heart disease if they consumed one serving (80 g) of F&V.[54] Findings from a cohort of adults (n = 7, 216; aged: 55-80 years) revealed that ≥ nine daily servings of F&V resulted in a 0.60 hazard ratio for CVD compared < five daily servings.[55] A 6-week randomized controlled trial conducted in adult men (n = 174) at risk for CVD demonstrated that two servings of high-flavonoid

F&V resulted in a reduction in the inflammatory marker, CRP. Additionally, four servings of high-flavonoid F&V was shown to increase plasma nitric oxide (NO), a potent vasodilator. Regardless of flavonoid content, increases in F&V resulted in less arterial stiffness, and mitigated reductions in NO.[56] Findings from a pilot randomized controlled crossover trial examining the impact of nitrate-rich green salads in postmenopausal women (n = 10; aged: 47-57 years) demonstrated that a 10-day consumption of green salads twice daily resulted in improvements in fasting plasma nitrate/nitrite concentration and brachial artery flow-mediated dilation, markers that have been indicated in cardiovascular health.[57]

Early adoption of F&V is particularly advantageous as F&V consumption is inversely associated with central obesity in adolescent populations.[58] Indeed, a representative sampling of adolescents enrolled in the Third National Health and Nutrition Examination Survey (n = 1,803; aged: 12-16 years) found that adolescents who met the criteria for central obesity (i.e., waist circumference for age and sex $\geq 85^{th}$ percentile) reported significantly fewer servings of F&V compared to adolescents in the lowest central adiposity quartile.[58] Further, F&V consumption has been linked to reduced inflammation, oxidative stress, and risk for CVD in adolescents.[59,60] Among young adults (18-30 years), F&V consumption has been associated with reduced oxidative stress 15 to 20 years later.[61] These findings are suggestive of the long-term relevance of F&V when adopted in early adolescence and adulthood. Moreover, early adoption of a plant-based diet is linked to healthier diet profiles later in adulthood as well as reduced CVD risk.[62]

Saturated Fat. Dietary saturated fat, typically found in items including butter, cheese, and red meats has been shown to increase total cholesterol and LDL

cholesterol.[63–65] Considering that total cholesterol and LDL have been associated with risk for chronic health conditions including CVD,[66] the 2015-2020 DGA recommends less than 10% of total daily calories from foods containing saturated fat.[67] Further, for individuals with known CVD or elevated levels of LDL cholesterol, intake from foods containing saturated fat should be closer to 7% of total daily calories.[68] A review of 15 randomized control studies (n = 59,000) found that reducing dietary saturated fat may be responsible for approximately 17% reduction in CVD risk.[69] Additionally, the authors reported that substituting dietary saturated fat with starchy foods or polyunsaturated fat may be beneficial to health.

Added Sugars. Added simple sugars, typically found in items including breakfast cereals, ketchup, sugar-sweetened beverages, candy, and baked goods such as cakes and other desserts, have been associated with adverse health outcomes. According to the WHO, excess consumption of added sugars from sugar-sweetened beverages has been associated with an increased risk of weight gain.[70] Alarmingly, the association between sugar-sweetened beverages and obesity has been observed in both children and adult populations,[71] and in addition to weight gain, excess consumption of sugar-sweetened beverages has also been associated with risk for T2DM.[72–74] The WHO also reported that excess added sugars are negatively associated with micronutrient intake, and low satiety.[75]

Importantly, research to date has found a positive association between a reduced consumption of added sugars and obesity, the risk for T2DM, and insulin resistance.[76,77] Considering these data, the 2015-2020 DGA recommends that Americans limit their intake of added sugar to 10% of total daily calories.[78]

Mediterranean Eating Plans. Mediterranean eating plans are rich in fruits and vegetables, whole grains, legumes, nuts, and healthful fats such as from olive oil and fish including salmon, and this diet also emphasizes the use of spices and herbs in place of salt for flavoring foods.[79] The Mediterranean diet has consistently been shown to positively impact waist-to-hip ratio, reduce markers of inflammation, and improve overall cardiovascular health.[80] In the Lyon Heart Study, it was shown that following a CVD event, individuals randomized to receive a Mediterranean eating plan were less likely to experience another CVD event or even death for up to four years.[80] Another RCT, the PREDIMED study which compared the effects of a low-fat diet to the Mediterranean diet, indicated a significant reduction in CVD following a Mediterranean eating pattern over a low-fat diet.[81]

Interest in Mediterranean eating patterns has been a focus of researchers and healthcare practitioners for decades. Beginning with the Seven Countries Study which began in 1947, American physiologist Ancel Keys and colleagues sought to understand the role of eating patterns and lifestyle factors on chronic disease risk in adult men (40-59 years old) residing in the U.S., Japan, Italy, Greece, the Netherlands, the Federal People's Republic of Yugoslavia (a.k.a. Yugoslavia), and Finland. In this prospective study, Keys and colleagues followed sixteen cohorts of men and hypothesized that coronary disease rate would differ based on lifestyle factors and physical activity levels at both the individual and population level.[82] Findings from this landmark study revealed a strong and positive association between levels of serum cholesterol and chronic heart disease (CHD) mortality where higher levels of serum were indicative of increased risk for CHD.[83] Further, the Seven Countries Study set the stage for a number of highly cited

research undertakings including the Healthy Aging: a Longitudinal Study in Europe (HALE) project and the Zutphen study. Findings from the Hale study, which began in 2001, indicated that adherence to a Mediterranean eating pattern was associated with a 29% reduction in risk of chronic disease mortality, and a 39% reduction in risk for coronary mortality.[84]

In young adults, adherence to Mediterranean eating patterns may also be protective against chronic disease development. Specifically, a study examining CVD risk biomarkers in young adults (n = 487; aged: 20-25 years) found that participants who most closely adhered to Mediterranean eating patterns exhibited a trend towards lowered arterial stiffness (measured as PWV) compared to non-adherers who tended to have higher LDL cholesterol, systolic and diastolic blood pressure, and lower HDL cholesterol.[85] Additionally, findings the Coronary Artery Risk Development in Young Adults study (n = 4, 713) showed an inverse relationship between Mediterranean eating patterns and the 25-year incidence of MetS further highlighting the long-term cardioprotective properties of Mediterranean eating patterns rich in F&V, whole grains, nuts, and fish.[86]

Nuts. There is compelling evidence to suggest that nuts, a component of Mediterranean eating plans, is beneficial to health. Early cohort studies such as the Physician's Health Study, the Adventist Health Study, the Nurses' Health Study, and the Iowa Women's Health Study all indicate that nut consumption confers cardioprotective benefits.[87–90] These epidemiologic studies show an 8.3% average reduction in risk for chronic heart disease death following each weekly serving of nuts.[91] In the Adventist Health study (n = 31, 802), participants consuming nuts more than four times per week

had fewer fatal CHD events and fewer non-fatal myocardial infarctions compared to participants who consumed nuts fewer than one time per week.[87] Males (n = 21,454) enrolled in the Physician's Health Study had a significantly reduced risk for sudden cardiac death and total coronary heart disease death if they consumed nuts two or more times per week.[88] Emerging experimental studies have also demonstrated benefits of nut consumption for individuals with T2DM. Specifically, a 12-week randomized crossover pilot study (n = 19) found that regular ingestion of one serving (28 g) of almonds at meal-time resulted in a 4% reduction in hemoglobin A1c thereby highlighting the favorable effects of almonds on long-term markers of glucose control in individuals with T2DM.[92] Similarly, a 12-week randomized parallel-arm pilot study (n = 11) found that daily almond consumption reduced CRP, a marker of inflammation, in individuals with T2DM despite the absence of modifications to diet or physical activity.[93]

Nut consumption has also shown similar benefits in adolescents and young adults. Particularly, a cross-sectional analysis of NHANES data from 2003-2012 on U.S. adolescents (n = 2,805; aged: 12-19 years) indicated that consumption of nuts (≥5 g/d) is independently associated with lower odds for MetS.[94] Similarly, nut consumption in young adulthood has been associated with a 19% and a 21% risk reduction for hypertension and low HDL cholesterol, respectively. Furthermore, improved nutrient intake, diet quality, CRP levels, and insulin were seen in nut consumers compared to non-consumers.[95]

Whole Grains. Whole grains, including brown rice, whole grain cereals, and bread, are components of the Mediterranean eating plans and provide fiber and are good sources of iron, magnesium, zinc, and B vitamins.[96] To date, whole grain consumption

has been linked to a number of favorable health effects, including a reduced risk for CVD and T2DM. A meta-analysis of 45 studies reported that three servings of whole grains (90 g) per day were associated with a relative risk of 0.81 for coronary heart disease.[97] A randomized controlled trial in middle-age individuals (n = 206) found that daily consumption of three servings of whole grains resulted in significantly reduced systolic and pulse pressure by 6 mm Hg and 3 mm Hg, respectively.[98] This reduction in systolic blood pressure could decrease the incidence of stroke and coronary artery disease by 25% and ≥15%, respectively. Whole grain consumption has also been indicated in body composition and glycemic control. Specifically, an 18-month randomized controlled study (n = 113) prescribing whole grains (e.g., rolled oats and rye) and pulses (e.g., lentils and chickpeas, etc.) found that participants randomized to the control arm of the study had greater fiber intake as well as a higher intake of vitamins and minerals, and a significantly greater reduction in waist circumference compared to the control group.[99] Next, a randomized controlled study investigating the effects of a Nordic diet (i.e., a meal plan high in fiber-rich whole grains, vegetables, and berries) found that, in mildly hypercholesteremic participants (n = 88), blood lipid profile and insulin sensitivity was improved following the 6-week trial.[100]

Greater whole grain consumption is associated with better intake of nutrients as well as healthier body weight in children and adults.[101] However, among college students, whole grains consumption is particularly lacking.[102] In a cross-sectional analysis of college students (n = 159), whole grain intake accounted for 0.7 servings per day despite that total grain intake was 5.4 servings per day.[103] Further, the authors reported that whole grain consumption was significantly higher in students with normal weight status

compared to those with overweight or obese weight status. Similarly, daily whole grain consumption was particularly low among two- and four-year college students.[104] Indeed, in a sample of young adults attending community colleges and universities in Minnesota (n = 1,015; mean age = 20 years), men attending community colleges consumed 0.84 serving of whole grains per day while their four-year counterparts consumed one serving of whole grains per day. Among female students, these values were even lower: 0.72 and 0.86 serving per day in community college and four-year university students, respectively.[104] Given the strong link between whole grain consumption and reduced risk for chronic diseases,[97] college students' low intake of whole grains places them at increased risk for disease development.

2. Indices for Assessing Diet Quality

The growing interest in assessing diet quality stems from the reality that free-living individuals consume combination diets comprised of multiple foods and food groups versus single nutrient-containing foods.[105] To date, more than 25 indices have been developed to assess diet quality.[32] While select indices focus on specific foods and/or food groups, other indices focus on food groups as well as the overall nutrient content of the diet.[32] Further, indices assessing diet quality based on specific foods and food groups typically focus on the intake of F&V, grains and cereals, and meat, dairy, and seafood.[106] Conversely, indices assessing diet quality based on nutrients typically focus on the consumption of total fat, the ratio of saturated fat to mono- or polyunsaturated fat, sodium, cholesterol, dietary fiber, and protein consumption.[106] In the U.S, assessment of diet quality is typically accomplished by several indices including the

Healthy Eating Index, the Alternative Healthy Eating Index, the Diet Quality Index, and the Rapid Eating Assessment for Participants [shortened version].[106–108]

Healthy Eating Index (HEI) 1995. The HEI, developed by the U.S. Department of Agriculture (USDA), was first introduced in 1995 to assess how well Americans' diets adhere to key recommendations set forth by the USDA's Food Guide Pyramid.[109] The HEI was based on 1989 and 1999 USDA data from the Continuing Survey of Food Intake by Individuals and was developed based on data from a representative sample of 3,997 individuals in 1989 and 3,466 individuals in 1990.[110] The HEI scoring system ranges from zero to one hundred with higher scores indicating better diet quality. In its original version, the HEI was used to assess diet quality based on ten components. The first five components assessed adherence to the USDA's Food Guide Pyramid for grains, F&V, milk, and meat while the other five components focused on consumption of total fat, saturated fat, cholesterol, sodium, and the variety of foods consumed within an individual's three-day diet.[110]

Healthy Eating Index (HEI) 2005. The HEI-2005 was the second installment of the original HEI developed in 2005. Like the HEI-1999, this updated index determined an overall diet quality score based on overall compliance to Federal dietary guidelines.[111] The primary reason for updated the HEI was based on the release of the updated Dietary Guidelines for Americans in 2005. The standards of the HEI 2005 were represented as a percent of 1,000 calories. The components of the HEI-2005 are total fruit intake, whole fruit, total vegetables, dark green and orange vegetables, and legumes, total and whole grains, milk, meat and beans, oils, saturated fat, and sodium.[111]

Healthy Eating Index (HEI) 2010. A further updated version of the HEI, introduced in 2010, incorporated four changes compared to the previous version of the HEI.[112] Namely, green vegetables and beans replaced legumes as well as dark green and orange vegetables. Next, plant proteins and seafood were incorporated to capture specific choices from the protein group. Third, the oils and saturated fats group was replaced by a ratio of poly- and mon-unsaturated to saturated fatty acids to reiterate the recommendation to reduce total saturated fat. Finally, to assess over-consumption, the adequacy component titled total grains was replaced by a moderation component titled refined grains. It is worthwhile to mention that the HEI-2010 reflects the vegan, vegetarian, and omnivore versions of the USDA Food Patterns.[112] The USDA Food Patterns was developed to help individuals meet Dietary Guidelines recommendations by identifying daily amounts of foods, in nutrient-dense forms, from each of the five major food groups and their subgroups.[113]

Healthy Eating Index (HEI) 2015. The HEI-2015 is the most recent iteration of the index. The HEI-2015 incorporated several changes. Since the 2015 Dietary Guidelines emphasized a reduction of added sugars, the HEI-2015 replaced the empty calories component with the saturated fat and the added sugars categories. Further, this is the first version of the HEI in which daily consumption of added sugars was to be kept at less than 10% of the total daily intake.[114] Additionally, the HEI-2015 replaced the solid fats category with the saturated fatty acids category for the purpose of calculating a standard.[114] The HEI-2015 also removed alcohol as a separate component in the diet and instead added it to the overall caloric intake for the day.[114] A recent publication that sought to evaluate properties of the HEI-2015 demonstrated evidence that support the

reliability, construct validity, and criterion validity of the index.[115] However, it is important to note that administering the HEI-2015 can be time-consuming, and that training is required to calculate a final score since each component of the index is comprised of multiple subgroups.[116] For example, within the adequacy component, calculations are required for 15 subgroups, including legumes. Further, across laboratory comparisons of scores may be a concern due to the subjective nature of calculations.[117]

Alternate Healthy Eating Index (AHEI). As with the HEI, the AHEI was intended to assess overall diet quality.[118] The AHEI was created by McCullough and colleagues in 2002 and focused on nine dietary components.[28,118] The AHEI was developed with the overarching goal of targeting food choices and macronutrient sources that were associated with reduced risk of chronic diseases. Key differences between the HEI and the AHEI are that the AHEI focuses on fat quality, alcohol intake, fiber from cereal, the duration of multivitamin use, and the ratio of red to white meat consumption.[118] As with the HEI, higher AHEI scores indicate better adherence to dietary guidelines.

Rapid Eating and Activity Assessment for Patients (REAP). The REAP questionnaire was designed to be completed quickly to allow rapid assessment of diet.[119] Unlike the HEI and AHEI which require participants to complete diet records over the course of one or more days, diet analyses using professional software applications, and trained personnel to assess the foods and nutrients consumed against the HEI guidelines, the REAP questionnaire is written at a sixth-grade level, can be self-administered, and takes approximately 10 minutes to complete and an additional few minutes to score. The REAP questionnaire was intended to help primary care physicians and other health care

providers quickly assess patients' diet and physical activity, and to facilitate brief counseling by the physician based on findings from the questionnaire.[119] The REAP was developed by investigators involved in the Nutrition Academic Award who were tasked with designing a tool to improve nutrition training across medical schools in the U.S.[119] In its original form, the REAP questionnaire consists of five objectives: One, to address dietary concerns of national nutrition priority in adults. Two, to provide a tool that could be completed following a brief interview by the provider or staff or that could be self-administered by patients. Three, to allow providers to easily assess patients' eating habits and provide tailored nutrition advice during an office visit. Four, to allow physicians to highlight patients' nutrition concerns that necessitate referral to a dietitian. Five, to create a nutrition profile for patients that can be included in their medical record.[119] Further, the REAP questionnaire consists of 32 questions with 27 of those questions focusing on the consumption of F&V, whole grains, calcium-rich foods, sugary beverages and foods, alcoholic beverages, sodium, and fat, saturated fat, and cholesterol. The remaining questions assess physical activity as well as issues regarding food shopping, preparation, food limitation, special diets, and a willingness to alter eating habits.[119] A study that evaluated the feasibility of REAP in 61 medical school students and practitioners found that practitioners rated REAP as practical, easy to use, and effective in accessing patients' diet and offer nutrition counseling. Despite these findings, REAP has not been widely adopted in research settings.[108]

Rapid Eating Assessment for Participants [shortened version] (REAP-S).

REAP-S is an abridged version REAP, which was originally developed to help providers rapidly perform diet assessments in fast-paced clinical settings.[108] Commonalities

between REAP and REAP-S are that both indices assess the intake of calcium-rich foods, whole grains, F&V, total and saturated fat, dietary cholesterol, sodium, sugar-sweetened foods and beverages, and alcohol consumption. However, unlike REAP, REAP-S does not inquire about physical activity. Additionally, unlike diet quality indices such as the HEI-2015 that require trained personnel to appropriately interpret and score the data, REAP-S can be completed in five or fewer minutes. Finally, scoring of REAP-S is straightforward: responses of 'usually/often' receive one point while responses of 'sometimes' and 'rarely/never or does not apply to me' receive two and three points, respectively.[116] This standardized scoring procedure reduces bias among investigators and laboratories. Since its inception in the early 2000s, two studies have assessed the validity of REAP-S, and one known study has utilized REAP-S to assess diet quality in U.S. adults.

In a validation study of REAP-S, Segal-Isaaacson and colleagues recruited first-year medical students from the Albert Einstein College of Medicine in New York.[108] Findings from this undertaking revealed that REAP-S was useful to estimate F&V, milk, fat, cholesterol, sugar, and fiber consumption. In Kurka's validation study, 224 collegiate male athletes and 166 collegiate female athletes completed REAP-S.[120] Using principal component analyses, a statistical method to identify patterns between groups, REAP-S demonstrated construct validity for identifying dietary patterns in athletes and was effective for differentiating dietary habits between athletes participating in aesthetic sports (e.g., gymnastics, and swimming) and those participating in non-aesthetic sports (e.g., golf, and water polo).[120]

In a secondary analysis conducted by investigators at ASU to examine the relationship between REAP-S and the HEI-2010 for scoring diet quality in healthy adults, both REAP-S and the HEI-2010 were related to nutrient intake, BMI, blood pressure, triglyceride concentration, and fasting plasma glucose.[116] Further, in their analysis, Johnston et. al reported that along with the HEI-2010, REAP-S was significantly correlated with indicators of diet quality, including NFR9.3, PRAL, and urine pH. Interestingly, REAP-S appeared to be more strongly correlated with these indicators of diet quality compared to the HEI-2010 ($r = 0.406$ and $r = 0.321$ for REAP-S and the HEI-2010, respectively). Finally, unlike the HEI-2010, REAP-S was correlated with plasma vitamin C concentration, an additional indicator of diet quality. These findings, combined with the relative ease of completing REAP-S and the low-cost associated with the questionnaire, highlight REAP-S as a valuable index to rapidly assess diet quality with practical utilization in research settings.[116]

Other Indices of Diet Quality. Diet quality scores can also be calculated based on the DASH Diet, the Alternate Mediterranean Diet (AMD), and the Alternate Healthy Eating Index-2010 (AHEI-2010). Specifically, there are four known scoring systems based on the DASH Diet: Dixon's DASH Diet Index, Mellen's DASH Diet Index, Fung's DASH Diet Index, and Günther's DASH Diet Index.[121] While the focus of each index varies slightly, all indices are effective for capturing how well eating plans align with the DASH eating pattern.[121] Next, scoring for the AMD diet is based on nine components, including total F&V except for potatoes, whole grains, nuts, alcohol, and red and processed meats.[122] Scoring for the AHEI-2010 is based on over 15 components, including total and whole fruit, sugar-sweetened beverages and fruit juice, seafood and

plant proteins, and empty calories.[123] Regardless of the scoring system, higher scores are indicative of eating patterns that are of higher diet quality.

3. Diet Quality, Disease Etiology, and Mortality

The relationship between diet quality, disease etiology, and mortality is complex. Findings from epidemiological undertakings suggest that eating patterns with lower diet quality scores are associated with more disease onset and premature mortality compared to eating patterns with higher diet quality scores.[124] A recent study assessing associations between changes in diet quality and total and cause-specific mortality among women in the Nurses' Health study and men in the Health Professionals Follow-up Study found that improved diet quality was consistently linked to a reduced risk of death in these populations.[124] Specifically, the investigators reported that a 20 percent increase in diet scores, as measured by the Alternate Healthy Eating Index and Alternate Mediterranean Diet, was significantly associated with a 7-15% reduction in CVD-specific mortality. Additionally, a 20 percent increase in diet scores, as measured by the AHEI, Alternate Mediterranean Diet (AMD), and DASH Diet, was associated with an 8-17% reduction in total mortality. Further, when compared to participants with low diet scores, participants with consistently high diet scores over a 12-year period saw a 14% reduction in risk of death from any cause when assessed with the AHEI score, 11% when assessed with the AMD score, and 9% when accessed by the DASH score.[124] A similar study which sought to examine associations between diet quality scores as assessed by various diet quality indices (e.g., the DASH Diet Score, the Healthy Eating Index-2005, the Mediterranean Diet Score, the AHEI Score, and the AHA Diet Score) and cardiometabolic risk in Puerto Rican adults (45-75 years old) over a 2 year period found that the Mediterranean Diet

score was associated with more favorable cardiometabolic profiles. Specifically, the Mediterranean Diet score was significantly associated with lower waist circumference, insulin, CRP, and BMI compared to the other diet quality indices.[125]

4. Eating Patterns of College Students

Weight Changes and the Transition to College. It has been shown that the prevalence of obesity increases with age,[126] and even for individuals within healthful weight parameters, prolonged consumption of unhealthful foods is associated with major health concerns, including T2DM, heart disease, and hypertension.[127,128] Enrollment in college marks a significant period of change for young adults. As these young adults enter a world of greater independence, exposure to new experiences, time away from parental units, and greater dependence on peer networks, notable changes occur that often result in increases in body weight and weight perceptions that contribute to a desire for weight loss.[9,129,130] While early studies have demonstrated weight gain upwards of fifteen pounds, referred to as the freshman fifteen, a 2009 meta-analysis focused on 24 studies between 1985 and 2008 reported that, of the pooled sample of 3,401 cases, the average weight gain during the freshman year was 3.86 pounds.[129] A more recent meta-analysis focused on 22 studies from 1980-2014 reported a pooled mean weight gain of three pounds over an average of five months.[9] Despite that 60.9% of college students experience weight gain during their first year of college,[9] increases in weight is not restricted to the first year in college. A recent examination of weight trajectories in university students found that students continue to gain weight throughout their college experience.[11] Further, the most updated report from the ACHA-NCHA survey found that one in three college students have overweight or obesity, and when compared to the

general population, weight gain during college is typically faster, and in some instances, five times higher than weight gain experienced in the general public.[9,10] Given that prolonged and excessive weight gain may result in obesity, and that obesity during adolescence is a predictor of obesity in adulthood,[131,132] added to the fact that obesity is a risk factor for several chronic conditions including T2DM and CVD, it is imperative to design robust interventions to improve the health of college students.[128,133,134] Further, given that habits formed during college typically extend into adulthood,[135] the Surgeon General's Vision for a Healthy and Fit Nation has identified universities as sites to promote awareness of health behaviors including healthful eating, weight control, and regular engagement in physical activity.[136,137]

Chronic Disease Risk in College Students. Chronic disease risk is understudied in college students. However, from among the available studies, it is evident that college students are at risk for these conditions. Indeed, a 2004 cross-sectional study of college students (n = 163; aged: 18-24 years) reported that 10% of participants had elevated levels of total or HDL cholesterol, or both and that 6% had pre-diabetes.[138] Further, the investigators reported that the risk of experiencing at least one component of MetS was threefold if an overweight phenotype was present. In another cross-sectional assessment of students (n = 300) enrolled at a university in Kansas, 24% of students had low levels of HDL cholesterol while another 9% had impaired fasting glucose and elevated triglyceride level.[139] In a larger (n = 2,722) cross-sectional study from 2005-2008, MetS was identified in 12.9% of college students.[140]

A more recent study demonstrates that metabolic abnormalities are still an issue in the college population. Specifically, from among a sample of students attending a

Midwestern university (n = 462), 33% of participants have at least one metabolic abnormality while 6% had two or more.[21] Additionally, 22% and 12.6% of students had high waist circumference and elevated serum triglycerides, respectively. Considering that MetS is significantly associated with a 1.5-fold increase in all-cause mortality, and a two-fold increase in cardiovascular outcomes,[141] not to mention other chronic conditions,[142,143] reducing metabolic abnormalities before they advance to MetS and subsequent chronic disease is of utmost importance.

The College Food Environment. The food environment present on and around college campuses is generally filled with a plethora of energy-dense, nutrition-poor, and highly processed meal and snack options.[144–146] Research to date indicates that the college food environment predicts the meal choices that students make. Specifically, a cross-sectional study conducted on food offerings on and around two colleges (i.e., one community college and one public university in Minnesota) found that, among students (n = 1, 059; mean age = 22 years), food was typically purchased three or greater times per week from at least one campus dining venue.[144] Further, given that 45% of college students reported meal purchases, it was revealed that, when compared to meals brought from home, higher frequency of meal purchases were associated with reduced consumption of breakfast as well as a higher intake of sugary and high-fat items.[144] Interestingly, many campus dining venues offered items similar to those offered at fast-food eateries, including pizza, French fries, and burgers. Not surprisingly, prolonged consumption of energy-dense items typically found in fast-food establishments has been linked to significant weight gain and poorer diet quality compared to nutrient-dense items such as fruits, vegetables, and whole grains.[147–153] Another assessment conducted on the

influences of college dormitory assignment found that, in females, assignment to dormitories with dining halls opened 7 days a week was associated with a 1 pound higher weight gain compared to females assigned to other dormitories. Interestingly, the presence of a grocery store within close proximity of the campus was associated with less weight gain over a one-year period.[145] It has also been shown that college students perceive ease of access to junk-food items, the convenience of unhealthful food and beverage items, and the high cost of healthful foods as barriers to healthful eating.[146]

Sleep, Meal Frequency, and Meal Timing in College Students. Sleep, meal frequency, and meal timing are concerns for many college students.[154–160] Previous research on the prevalence of insomnia in college students has ranged from 9.4-47%.[161–163] Further, students who experience insomnia are typically at increased risk of maladaptive eating.[155] Along with insomnia, college students experience a number of sleep-related conditions including insufficient sleep, mild to severe sleep disorders, and reduced sleep quality.[157] Indeed, it has been shown that 27% of college students are at risk for at least one sleep disorder while poor sleep quality (i.e., < 7 hours of nightly sleep) is experienced by >25% of college students.[156,157] Further, sleep insufficiencies have been linked to issues with meal timing and meal frequency. For instance, when compared to students who slept ≥ 8 hours per night, those with less than 8 hours of sleep experienced significantly more binge-eating episodes, reduced internal regulation of food, and increased negative attitudes toward food.[157] Conversely, students who report better overall sleep quality are more likely to exhibit traits of a competent eater, including a higher intake of foods high in fiber and required vitamins and minerals.[157,164,165] Low-eating competence is associated with overweight status.[157] Similarly, later sleep times

have been associated with increased consumption of sugar-sweetened beverages, energy drinks, fast food, poorer academic performance, overall health, and attention deficits.[156,160,166–168] Finally, students with better sleep practices, including earlier bed-times, reported better social and physical wellness, improved academic performance, and overall higher grade point averages compared to students with insufficient sleep.[168,169] Regarding meal frequency, prospective studies have demonstrated a significant increase in risk for disease following high meal frequency; ≥6 meals/day compared to low meal frequency (1-2 meals/day).[170] A 52-week randomized controlled trial conducted on participants (n = 140) found an inverse relationship between HDL and the number of snacks consumed per day.[171] Conversely, a 16-week crossover pilot trial examining the effects of three meals per day compared to 1 meal per day (without overall caloric reduction) in normal-weight adults (n = 15) found that while participants were able to comply with the one meal per day regimen, they reported a significant increase in hunger.[23] Further, while a reduction in fat mass and improvements in HDL cholesterol and cortisol concentration were observed, participants also had a significant increase in blood pressure, and total and LDL cholesterol. These findings demonstrate that while one meal per day may result in some cardiovascular benefits, it may not be acceptable for the general population.

Nutrition Knowledge and Meal Decisions in College Students. Overall, college students possess a working knowledge of basic nutrition principles.[135,172] Specifically, a cross-sectional assessment of weight status, dietary habits, physical activity, dietary beliefs, and nutrition knowledge among college students attending a university in Michigan reported that students had ‘satisfactory’ nutrition knowledge and that female

students had higher nutrition knowledge scores compared to male students.[135] These findings align with a recent cross-sectional examination of the nutrition knowledge of college students which reported that almost 88% of college students agree that sodas are unhealthful, 61.2% believe that processed foods contain additives and artificial ingredients, and 89.3% of students agree or strongly agree that the consumption of highly-processed foods is deleterious to health.[172] Despite that college students possess some general nutrition knowledge, it is important to note that this knowledge often does not extend to the meal decisions that students make. For instance, 65% of students consume processed and convenience meals, including cereal, chips, and cookies daily, and in some instances, multiple times in a 24-hour period.[172] Finally, it is relevant to note that consumption of energy drinks, as consumed by almost 18% of college students, has been associated with decreased self-reports of F&V consumption as well as increased consumption of sodas and frozen meals.[173]

Fruit and Vegetables, Nuts, and Whole Grain Consumption in College Students. According to the CDC's 2018 version of the State Indicator Report on F&V consumption, the majority, 88% and 91%, of adults do not meet the daily recommendation for F&V intake, respectively.[174] These findings are somewhat similar to those observed in college students. In 2013, a report from the American College Health Association-National College Health Assessment (ACHA-NCHA) indicated that the majority (93.7%) of college students failed to consume the daily recommendation for F&V.[135] While this amount appeared to be less in study of college students in 2015, 84% vs. 93.7%,[175] it is imperative to note that only 106 students were included in the final analysis making generalization difficult. Alarmingly, the most updated report from the

ACHA-NCHA indicates that since 2013, the number of college students who fail to consume adequate amounts of fruits and vegetables has increased from 93.7-96% suggesting that while adequate F&V consumption is linked to health improvements including better diet quality, a reduced risk for T2DM, CVD, obesity, and depression,[21,176–178] college students generally do not meet the daily recommendations for fruit and vegetable intake. Along with fruit and vegetable intake, college students do not meet the daily recommendation for whole grains. In a sample of students (n = 159; mean age: 19.9 years), whole grain consumption was significantly lower in students with normal weight compared to those with overweight or obesity. Additionally, while the intake of grains equaled 5.4 servings per day, whole grain intake only accounted for 0.7 of those servings.[103] While there are no known studies examining the prevalence of nut consumption in college students, an 8-week study examining the effects of walnut consumption on verbal and non-verbal reasoning in college students (n = 64) found that walnuts were effective for increasing inferential verbal reasoning.[179] Interestingly, among college students, lack of motivation, high cost of F&V, lack of involvement in meal preparation, stress, time constraints, and the convenience of low-cost, high-calorie food and snack items are often cited as barriers to the consumption of healthful foods.[11,146,175]

5. History of Fasting

Fasting is the practice of abstaining from food and beverages for religious, spiritual, political and/or health reasons.[180] Fasting typically involves fasting for an extended period of time, usually 16–48 hours, with little or no caloric intake followed by periods of ad libitum consumption.[181,182] Depending on the type of IF protocol, the time spent fasting as well as the allowable caloric consumption during the fasting period can

vary significantly.[181,182] In ancient Greece, inhabitants fasted to prepare for rituals and to ward off demonic forces,[183] while Christians and Muslims viewed fasting as a valuable practice to prepare for holy revelations[184] or to increase self-control.[185] Early proponents of fasting to promote health include E.H. Dewey, a mid-eighteenth century American physician who believed that all diseases originate from prolonged excess consumption, and Upton Sinclair, a writer and political activist who wrote several books including *The Fasting Cure* which highlights the health benefits of fasting.[186,187]

Landmark studies beginning in 1963 have demonstrated the early efficacy of fasting regimens to improve dietary habits and reduce weight.[188,189] Indeed, a study published in 1963 found that a 48-hour fast followed by a stepwise re-introduction of calories (separated into six daily meals) resulted in weight loss without regain for up to six months.[189] A surprising finding was that, following the fasting regimen, patients reported less desire to select high-carbohydrate foods as well as a loss of compulsion to eat. Next, a study conducted on patients with morbid obesity (n = 207) found that following a prolonged fast (approximately two months), mean weight loss was 28.2 kg while participants who observed the fasting protocol for greater than two months saw a mean weight loss of 41.4 kg.[188] Further, over a 7.3 year follow-up period, participants (n = 121) maintained their weight loss for the first 12-18 months after which point weight regain was similar between all participants except for individuals with pediatric-onset obesity who saw weight regain in excess of their original weight.[188]

Intermittent Fasting. Intermittent fasting (IF) is a hypernym for eating patterns whereby individuals voluntarily abstain from food and beverages during designated fasting periods, followed by the consumption of caloric-containing items during feeding

periods.[22] Following the favorable findings from Gordon and colleagues' undertaking in which a 48-hour fast resulted in weight loss and improved dietary habits,[189] Stewart et al. measured the effects of prolonged fasting in a male patient weighing over 200 kg.[190] During the nineteen-month treatment, total fasting (i.e., zero caloric intake) occurred for ten consecutive days alternating with ten consecutive days of low caloric intake for a total of 290 days of total fasting. Following the treatment, the patient lost 96.2 kg, 65 cm around his waist, and 66 cm around his chest. A PubMed inquiry revealed that 72 scientific articles were published on IF in 2018, and a recent Google search for 'Intermittent Fasting' yielded 553,800,000 results. Further, over 1,000 books have been written on the potential health benefits of IF including titles specifically for beginners, women, athletes, and vegetarians. Although the popularity of this ancient practice has grown both in the media and in research arenas,[191] the number of randomized clinical trials conducted in humans is relatively low.

Types of Intermittent Fasting Regimens. To date, several IF protocols have been linked to health benefits including weight loss and improvements in biomarkers linked to T2DM and CVD.[22] Examples include the alternate-day fasting, and TRF.[22,192,193] Alternate-day fasting (ADF) refers to fasting regimens whereby individuals consume roughly 25% of their daily energy needs during a fasting day and ad-libitum consumption of calorie-containing food and beverages during feeding days.[192,193] TRF refers to fasting protocols that allow ad-libitum consumption of calorie-containing food and beverages during specific time periods followed by routine fasting periods.[22] An important distinction of TRF compared to other IF protocols is that TRF regimens do not restrict daily caloric intakes; rather, all caloric intake is restricted to a daily, pre-determined

feeding interval.[22] While feeding and fasting intervals differ among TRF regimens, typical TRF regimens extend traditional nighttime fasting routines observed by typical adults.[22]

6. Intermittent Fasting and Health

Intermittent Fasting and Weight. Both animal and human trials have shown that IF can result in weight loss. In animal models examining the effects of TRF (i.e., routine ad libitum consumption of calorie-containing foods and beverages during restricted time periods), feeding windows have ranged from 3-12 hours while study durations have ranged from 4-18 weeks.[194–197] Despite this variance in feeding window and study duration, weight loss has ranged from 0-28 %.[194,198] Interestingly, Sherman et al.'s examination of a 3-hour TRF protocol over a 16-week period showed that mice contained to the intervention group saw a 9 % lower body weight than mice contained to the control group (liberated feeding) despite similar consumption of caloric intake between the groups.[194] The finding that weight loss is significantly more in TRF mice compared to control mice despite similar caloric intake is supported by Hatori et al., whose 8-9 hour TRF protocol over the course of 16 weeks yielded a mean weight loss of 28 % more in mice contained in the intervention group compared to the control group.[198]

Human trials examining the impact of TRF on weight parameters have included feeding windows between 4-12 hours and studies ranging from 2-12 weeks.[24,199] Collectively, mean weight loss has ranged from 0-5%.[199,200] In a 2007 randomized, crosover study, Stote et al investigated the impact of reduced meal frequency on glucose regulation utilizing two 8-week feeding protocols separated by an 11-week normal diet regimen.[23] The two 8-week feeding protocols consisted of participants consuming a

single meal daily between 5-9 PM (INV) and the traditional three meals per day without restriction on eating time (CON). During the trial, participants could consume unlimited amounts of calorie-free items, including water, coffee without milk, cream or sugar, and diet sodas. Findings from this undertaking indicated that, for both non-obese adult men and women (n = 15; aged: 40-50 years), TRF significantly reduced fat mass and body weight.[23] Next, while Ravanshad et al. and Aksungar et al. found no changes in weight loss in male and female participants,[201,202] a trial by Temizhan et al. reported a reduction in body weight by 5 % following a 4-week TRF intervention.[200] These findings are interesting considering that the duration of the TRF intervention was similar among the three researchers.

Next, a study examining the impact of meal timing on weight parameters found that, among participants (n = 420), individuals who followed a 20-week intervention whereby lunch was consumed before 3 PM saw faster and more significant weight loss compared to individuals who consumed lunch after 3 PM.[203] The authors also reported that, when compared to early eaters, late eaters were more likely to skip breakfast. These findings are in alignment with studies conducted on shift-workers who, despite consuming similar quantities of calories,[204] were more likely to experience weight increases and poorer health outcomes including increased inflammation, impaired glucose metabolism, and risk for obesity, MetS, and CVD.[205] A proposed mechanism by which unusual meal timing can disrupt health stems from a disruption of the circadian system.[206] Indeed, in animals, it has been shown that correcting food intake (i.e., eating earlier in the day), can favorably impact metabolic disturbances despite the amount of fat in the meal.[198,207,208] Additionally, in humans, it has been shown that a breakfast

containing high amounts of carbohydrates and protein may prevent weight gain by suppressing the hunger hormone ghrelin.[209]

Intermittent Fasting, Blood Pressure, and Blood Lipids. Research to date indicates that IF may be protective against select biomarkers of cardiovascular health, including blood pressure and blood lipids.[22,210] Particularly, findings from animal research show that ADF is as effective as calorie restriction at reducing blood pressure, total cholesterol, and triglycerides.[211,212] In humans, ADF and other forms of periodic fasting have also shown some promise in terms of lowering blood pressure. In a statement issued by the American Heart Association, observance of ADF and other forms of period fasting resulted in reduced systolic and diastolic blood pressure, although these effects appear to be dependent on the overall amount of weight loss. Specifically, a ≥6 % weight loss appears to be associated with a reduction in systolic blood pressure by 3-8 % and a reduction in diastolic blood pressure by 6-10 %.[127] Next, in obese adults, a randomized controlled parallel-arm trial examining the effects of a 12-week ADF protocol alone or in combination with endurance exercise, exercise alone, or a control group found statistically significant reductions in systolic and diastolic blood pressure in adults adhering to the ADF protocol alone.[193] Despite the ability of ADF protocols to improve cardiovascular biomarkers, it is relevant to note that these eating patterns may not be sustainable as participants who have undergone ADF protocols report persistent hunger that did not improve over the course of the intervention.[213]

In addition to ADF, emerging research indicates that TRF may be promising to reduce blood pressure in humans. A proof-of-concept study conducted by Sutton et al. examining the effects of a 6-hour TRF protocol (with dinner prior to 3 PM) in adult men

with pre-diabetes demonstrated that, compared to the control group (12-hour feeding window), men randomized to the TRF group experienced a significant reduction in both systolic (mean = 11 mg Hg) and diastolic (mean = 10 mg Hg) blood pressure following the 5-week trial.[27] Similar findings were observed in a pilot study examining the impact of an 8-hour TRF protocol on weight and risk of metabolic disease in adults with obesity.[24] Specifically, Gabel et al. found that following their 12-week intervention, participants randomized to the intervention arm of the trial saw a reduction in systolic (mean = 7 mm Hg) but not diastolic blood pressure. This is despite that participants in the intervention group observed a 2.6 % reduction in total body weight over the duration of the trial.[24]

While ADF has been shown to effectively lower blood lipids in some human trials, findings from other undertakings have been inconsistent. Indeed, while a randomized controlled trial conducted on the impact of ADF in adults with normal weight or overweight status reported significant reductions in triglyceride concentration following a 12-week ADF intervention, the authors reported no changes in LDL cholesterol or HDL cholesterol.[214] Contrary to these findings, an 8-week ADF protocol did result in reductions in LDL cholesterol as well as triglycerides in participants with obesity.[215] When comparing the findings from Varady et al. and Bhutani et al., participants experienced greater weight loss following the 8-week ADF protocol compared to the 12-week ADF protocol (mean of 5.7 kg and 5.2 kg, respectively). Since reductions in triglycerides appear dependent on the total amount of weight loss, it is worthwhile to explore whether these findings hold for future interventions. While there are significantly fewer human trials examining the effects of TRF on blood lipids, a study

examining the effects of a 16-hour fast during the month of Ramadan found that among participants (n = 52; mean age: 33), levels of triglycerides and total, LDL, and VLDL cholesterol were significantly reduced.[200] Additionally, it was shown that greater improvements were seen in women compared to men. Specifically, men saw a 28.8 mg/dL reduction in triglycerides by while women saw a 26.6 mg/dL reduction. In terms of total, LDL, and VLDL cholesterol, men saw a reduction of 15.2 mg/dL, 12.6 mg/dL, and 5.2 mg/dL. Conversely, women saw a reduction of 19.4 mg/dL, 14.6 mg/dL, and 5.5 mg/dL for total, LDL, and VLDL cholesterol, respectively.[200]

Intermittent Fasting, Blood Glucose and Insulin Control, and Inflammation. Several animal studies utilizing ADF protocols report promising results, including improvements in insulin sensitivity, and reductions in inflammation. Specifically, Arum et al. reported significant improvements in insulin sensitivity in male rodents fed every other day compared to rodents who were fed ad libitum, daily.[216] Additionally, the authors contend that fasting reduced insulin-like growth factor and glucose levels.[216] Other studies conducted in healthy non-obese adults have demonstrated that an ADF protocol (observed for 1-22 fasting days; mean fasting day = 13) resulted in reductions in glucose and insulin as well as an increase in adiponectin and reduction in leptin.[199,213,217]

Along with ADF, findings from TRF trials conducted in animal models reveal that TFR can improve glucose tolerance and reduce inflammation.[198,211] A study by Hatori et al. examining the impact of a TRF protocol on diet-induced obesity over the course of >100 days indicated that the TRF protocol protected mice from the effects of a high-fat diet. Further, mice contained to the TRF group saw significant improvements in glucose tolerance, nutrient utilization, adiposity, motor function, and cholesterol.[198] In

other animal models, an association has been found between TRF regimens, glucose levels, and inflammatory markers including TNF-a and interleukin-6.[218]

Currently, the literature on human participants is severely limited, and findings on the effects of TRF for blood glucose and insulin control and inflammation are inconsistent. In terms of favorable outcomes, Sutton et al. demonstrated that a 6-hour early TRF protocol, whereby participants consumed dinner before 3 PM, was effective for improving insulin sensitivity, beta-cell responsiveness, and oxidative stress.[27] In their 5-week supervised feeding trial, men with pre-diabetes with poorer measures of baseline hyperinsulinemia experienced the largest improvements in insulin following the trial.[27] These findings are supported by previous research initiatives that point to the ability of IF to reduce insulin more effectively than blood glucose. Finally, in a recent investigation conducted in resistant-trained adult men (n = 34; mean age: 29.21 years), an 8-hour TRF protocol resulted in a significant reduction in fat mass, and insulin-like growth factor 1 after eight weeks compared to a typical diet protocol with a 12-hour feeding regimen.[26]

Contrary to these findings, other undertakings have demonstrated little to no effects of TRF on blood glucose or insulin control. For instance, in their investigation of the effects of an 8-hour TRF protocol in adults with obesity, Gabel et al., reported that, following a 12-week intervention, participants randomized to the TRF group saw no differences in fasting blood glucose or fasting insulin.[24]

Intermittent Fasting and Other Health Outcomes. Emerging research indicates that IF may be effective for other health concerns, including cancer, mood, and pain disorders.[29,219,220] A prospective study conducted to assess whether the length of a nightly fast predicted cancer recurrence and mortality in women with breast cancer found that

longer fasting periods (i.e., ≥ 13 hours per night) were associated with a reduced risk of breast cancer recurrence, but not mortality, compared to shorter fasting periods (i.e., < 13 hours per night). The authors also reported that each 2-hour increase in the total length of a nightly fast was associated with lowered hemoglobin A1c, and longer nighttime sleep.[219] Next, a study examining the effects of fasting on murine breast cancer allografts found that just two 48-hour rounds of fasting were as effective as two cycles of chemotherapy treatment with cyclophosphamide (150 mg/kg) to delay the progression of tumor growth in mice.[221] Additionally, the authors contend that through the action of reduced glucose, ketone bodies, and insulin, fasting improves the action of chemotherapy agents by making it difficult for cancer cells to survive.[221]

A pilot study examining the effects of a 6-hour TRF protocol in healthy college students enrolled at ASU found that, following the 4-week intervention, participants randomized to the TRF group reported significant improvements in mood, particularly anger.[29] Similar findings have been observed in individuals with chronic rheumatic conditions where medically supervised fasting protocols ranging from 7-21 days has been used to reduce pain.[220] Indeed, it is proposed that fasting protocols are associated with an increased availability of the neurotransmitter serotonin and endocannabinoids which have been shown to favorably impact a number of pathological conditions including neuropathic pain as well as mood and anxiety disorders.[220,222]

In another study examining the effects of resistance training only compared to resistance training with TRF in recreationally active men, Tinsley et al. reported greater improvements in upper and lower body strength as well as lower body muscle endurance and lean body mass in participants in the resistance training with TRF group.[210]

7. Proposed Mechanisms of Action for Intermittent Fasting

Circadian Biology and Satiety as Mechanisms for the Effects of IF. Nearly all species are governed by a biological clock that, if functioning properly, ensures physiologic functions and behaviors including metabolism and energetics, physical coordination, sleep, and hormonal secretion are performed at optimal times.[22,223–226] In human, this sophisticated circadian system is approximately 24 hours long and comprises both endogenous and peripheral clocks. While the master endogenous clock is located in the suprachiasmatic nucleus of the hypothalamus, other peripheral clocks have been identified on the liver. It has been shown that the master endogenous circadian clock is responsible for coordinating the actions of peripheral clocks via neural and humoral cues.[227] Further, the master clock also receives external input from light.[226] While the master clock is responsible for behavioral rhythms including sleep-wake and feeding cycles, metabolic processes including glucose tolerance, fat storage, insulin sensitivity, and oxidation of fatty acids are coordinated by peripheral clocks.[208,228] During periods of feeding, food, and beverage consumption provide energy substrates to maintain homeostasis.

Indeed, during feeding and activity, energy harnessed from glucose is primarily provided by the diet, while during instances of sleep and fasting, energy is liberated from stored energy substrates via the processes of glycogenolysis and lipolysis.[229] It is not surprising that periods of feeding align with hours of wakefulness, engagement in exercise or other high metabolic activities, and anabolism, while periods of fasting coincides with low metabolic activities, sleep, and catabolism.[229] Since the daily rhythm of food intake and energy metabolism are regulated by the circadian system,

misalignment of this system can negatively impact overall health in both animal models and human participants. While a functioning circadian system is linked to a decreased risk for disease as well as improved mood, metabolism, and sleep quality, a disrupted circadian system has been shown to increase disease risk and reduced sleep quality, metabolism, and mood. In rodents, researchers have identified several clocks that, when impaired, appear to result in metabolic disturbances.[229–231] In particular, an increase in glucose tolerance has been observed when the hepatic clock is disrupted.

Next, impairments in the pancreatic, muscular, suprachiasmatic, heart or adipose clocks have been associated with a decreased synthesis of insulin, altered muscular performance, altered insulin sensitivity, decreased cardiac efficiency, and increased adiposity, respectively. Additionally, even short-term circadian misalignment can result in reductions in sleep efficiency, and leptin and increased mean arterial pressure, postprandial glucose, insulin, and cortisol. Considering that cortisol is a key regulator of metabolism, increased cortisol levels present later in the day, as is the case in short-term circadian misalignment, can contribute to insulin resistance and hyperglycemia.[224,232,233] Further, a reduction in leptin has been associated with an increase in the desire to eat as well as decreases in energy expenditure while sleep deprivation has been linked to obesity, hypertension, and T2DM.[224,234–236]

Light, as perceived by the retina, is regarded as the most powerful trigger of the master endogenous clock located in the hypothalamus.[226] Exposure to prolonged to light (e.g., during nighttime hours) extends both the feeling of wakefulness and late-night consumption.[226,237] Structured feeding patterns, such as TRF that align with circadian biology may reduce chronic disease risk.[223–225,229,238–240] Conversely, nighttime eating,

such as the case with shift-workers, may increase the risk for obesity, select cancers, T2DM, and CVD.[241–244]

Research has demonstrated that excessive caloric consumption is associated with increases in BMI. Due to the nature of shift-work, meals are typically consumed outside of daytime hours; specifically, during nighttime hours, are usually higher in total calories, and are of poor diet quality.[204,205] Not surprisingly, it has been shown that night eating syndrome is associated with an increased risk of weight gain. Taken together, these factors result in chronobesity, a phenomenon in which metabolic disturbances result from a repeated desynchronization of the circadian system.[245]

In mice exposed to shortened light-dark cycles, there is an increased presence of CVD, total body mass, and insulin resistance resulting from a large insulin/glucose ratio. Aside from shift-workers, a study conducted in Korean adolescents (n = 1,738; aged: 12-18 years) found a positive correlation between nighttime meal consumption and less desirable dietary behaviors, including increased energy intake from snacks and fat. Further, the authors reported that in females, nighttime meal consumption was associated with increased BMI.[246] Similarly, studies in which sleep is shortened present a reality where the daily feeding period is lengthened and the risk for impairment of insulin sensitivity and glucose tolerance is increased thereby contributing to the risk for T2DM.[235]

In animal trials, structured TRF protocols appear to favorably impact the circadian system which has been shown to improve blood lipids, glucose, insulin, and select markers of inflammation.[22] An experimental trial assessing the effects of a TRF protocol without reduction of caloric intake found that, compared to mice in the high-fat diet

group, those in the TRF group had improved circadian clock oscillations which resulted in favorable gene expression affecting nutrient utilization and energy expenditure. Specifically, mice in the TRF group had improved motor coordination and were protected from inflammation, obesity, hepatic steatosis, and hyperinsulinemia despite that both groups of mice consumed approximately the same number of calories.[198]

Similarly, randomized controlled trials conducted in humans have found favorable health outcomes following TRF protocols. In particular, a crossover trial conducted in 15 (10 females; 5 males) normal-weight men and women (40-50 years old) over the course of eight weeks found significant improvements in HDL cholesterol.[23] Another crossover study conducted in 29 normal-weight men following an extended nightly fasting protocol (i.e., eleven or more hours) for two weeks separated by two weeks of usual nightly fasting also found significant reductions in body weight.[25] Interestingly, there were no significant differences between the intervention and control group for mood profiles, which support the notion that short-term reductions in total caloric consumption do not negatively affect mood in men following a TRF protocol. In a study assessing the effects of severe, short-term energy deprivation in healthy adults (n = 21; aged: 18-39 years), participants undergoing energy deprivation had postprandial increases in anorexigenic hormones (i.e., PP, and GLP-1) while ghrelin concentration was reduced suggesting that IF may suppress hunger and promote satiety.[247]

The Gastrointestinal Microbiota as a Mechanism for the Effects of IF. Select aspects of the gastrointestinal tract appear to follow a circadian rhythm.[191] For instance, gastric emptying and blood flow are greater during daytime hours, and responses to a glucose load are faster during the morning vs. the evening.[248] Additionally, research with

mice has revealed that the diversity of the gut microbiota fluctuates with the time of day.[249] In an animal study, normal cyclical fluctuations to the diversity of the gut microbiota were disrupted in mice with ad libitum access to a high-fat diet. Interestingly, TRF appears to restore some of the normal fluctuations to the diversity of the gut microbiota.[249] Given the association between the diversity of the gut microbiota and metabolism, it is not surprising that the gut microbiota has emerged as a potential mechanism whereby intermittent fasting can favorably influence health .[191]

Additionally, emerging research shows that IF is linked to favorable changes in the composition of adipose tissue, which may favor metabolic homeostasis. Specifically, Li et al. found that mice adhering to an IF protocol (i.e., fasted every other day) had an increase in beige fat development within white adipose tissue, which resulted in a reduction in insulin resistance and obesity.[191] The authors credit the reduction in insulin resistance and obesity to an increase in the beiging effect seen in white adipose tissue. Specifically, it appears that IF shifts the composition of the gut microbiota, which results in an elevation of fermentation agents such as acetate and lactate and the upregulation of monocarboxylate transporter 1 (MCT 1) expression. Taken together, these factors activate the beiging effect in adipose tissue. This beiging effect is particularly important as beige adipose tissue is reported to be metabolically more active than white adipose tissue which could account for the proposed improvements in metabolic health and obesity.[250,251]

In humans, the composition of the gut microbiota appears to differ between lean individuals compared to individuals with obesity. A study that compared the profiles of arabinogalactan and inulin (types of dietary fiber) fermentation in individuals with ‘lean

microbiota' and 'obese microbiota' found that while individuals with 'lean microbiota' and those with 'obese microbiota' have similar strains of bacteria, the quantity appears to differ.[252] Specifically, the authors reported that individuals with 'lean microbiota' had higher Bifidobacterium compared to individuals with 'obese microbiota' who had higher Clostridium. Specifically, when comparing the two profiles, individuals with 'lean microbiota' had 23% Bifidobacterium, 34% Clostridium, 14% Lactobacillus, and 13% Enterococcus while individuals with 'obese microbiota' had 10% Bifidobacterium, 46% Clostridium, 17% Lactobacillus, and 15% Enterococcus.

Modifiable Lifestyle Behaviors as Mechanisms for the Effects of Intermittent Fasting. In addition to circadian biology and the gut microbiota, modifiable lifestyle behaviors including energy intake, energy expenditure, and sleep have emerged as potential mechanisms whereby intermittent fasting protocols can improve health.[22] The majority of studies investigating the effects of alternate-day and modified fasting protocols have shown significant weight reduction following the fasting protocol. These findings suggest that weight reduction is an indirect measure of energy intake lending support to the premise that intermittent fasting protocols reduce weight as a result of lower caloric intake.[22] Since lowered body weight is typically associated with a high functioning circadian system, these findings support the notion of intermittent fasting as a nontherapeutic mechanism for health improvement.

Findings from animal studies indicate that the circadian system regulates locomotion. Indeed, mice experienced improvements in activity, energy expenditure, and overall muscle expenditure toward the latter end of the feeding period.[198] While no known human trials have directly assessed the impact of intermittent fasting on

locomotion, it may be prudent to consider these experimental designs in future investigations. Evidence is mounting on the importance of sleep as well as reports of lowered sleep quality and increased sleep disturbances in human populations. In the U.S. alone, between 50 and 70 million individuals suffer from at least one sleep disorder (e.g., insomnia or sleep apnea). Further, a report from the Centers for Disease Control and Prevention found that 35% of Americans do not meet the recommendations for adequate sleep (i.e., 7 hours per day).[253] The reduction in total sleep time typically results in increased feeding periods throughout the 24-hour day. Worse, late-night consumption may lead to disruptions in sleep, including reduced sleep duration and poor sleep quality; factors that, in observational studies, can lead to misalignment of the circadian system, which has been shown to increase postprandial glucose, and insulin. Collectively, desynchronizations of these glucoregulatory markers can lead to insulin resistance and an increased risk for obesity, CVD, and T2DM.[22]

Summary

Overall, a growing body of literature has been conducted to better understand the relationship between dietary patterns and chronic disease risk. Additionally, there are a number of studies that examine the effects of IF on disease risk. While many of these studies have been conducted using animal models or have been limited by modest sample sizes, findings have been favorable, suggesting that IF can be used as a non-pharmacologic intervention for chronic health conditions. Specific to TRF, previous research has demonstrated improvements in HDL and LDL cholesterol, weight, glucose, and systolic blood pressure in non-collegiate adults. Despite this forward progress, no known studies have directly assessed the effects of TRF on diet quality in college

students. Given that the typical college student's eating patterns consist of low quality offerings such as calorically-dense highly processed foods, and that prolonged unhealthful eating patterns place college students at risk chronic health conditions, the randomized controlled trial proposed herein provides a unique opportunity to utilize a TRF protocol to improve diet quality. Favorable findings could highlight TRF as a cost-effective and potentially sustainable strategy to improve health in this population.

CHAPTER 3

METHODS

Study Design

This randomized control parallel-arm study was conducted at ASU from October 2019 to April 2020. The primary outcome of this 8-week study was to examine the effects of a daily 18-hour fast vs. an 8-hour fast on diet quality (as measured by the Rapid Eating Assessment for Participants [shortened version] REAP-S questionnaire). Secondary outcomes were fasting resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures in college students enrolled at ASU. Institutional Review Board approval at Arizona State University (STUDY00010810; Appendix A) was granted prior to recruitment and commencement of study activities. The trial is registered at ClinicalTrials.gov (ID#: NCT04348019).

Participants

College students were recruited from ASU campuses. Written informed consent (Appendix B) was obtained by a trained member of the research team prior to the beginning of study activities. In-person and online flyers, email correspondences, and ListServs were used to recruit participants beginning in October 2019 and ending in January 2020. Recruitment flyers informed potential participants that the 8-week study was designed to assess the effects of two distinct fasting lengths on health: a daily18-hour TRF protocol and a daily 8-hour fast. Participants were also informed of potential risks, benefits, and withdrawal privileges during screening.

Inclusion Criteria. Participants were college students (≥18 years old) healthy by self-report, non-smokers (includes vaping), recreationally active (< 420 minutes of activity/week and not training for or competing in sports events), and free of acute illnesses or diagnosed chronic diseases (i.e., diabetes, heart disease, MetS) by self-report. Female participants were included if they had a regular menstrual cycle or were on hormonal contraceptives (i.e., birth control pills, IUDs, or patches) at the time of the study. Due to fluctuations in lipid levels between phases of the menstrual cycle (i.e., LDL cholesterol is reportedly higher during the follicular vs. the luteal phase),[254] females were required to visit the research laboratory within five days after self-reported menses onset. Additionally, subsequent visits were phase-aligned (i.e., held approximately one calendar month from the previous visit).[255] Participants were not excluded based on race/ethnicity or socioeconomic status.

Exclusion Criteria. Students who regularly fasted for >12 hours per day, adhered to a fasting regimen (e.g., alternate day fasting, Ramadan-style fasting, 5:2 fasting) at the time of screening or within six months of screening, those with weight loss attempt(s) (e.g., restricting calories, taking diet pills, etc.) within six months of screening, those with a history of weight cycling (i.e., repeated weight loss and weight gain over time), those who worked night-shifts (i.e., midnight to 6 AM) at screening, those unwilling to adhere to the fasting protocol including maintaining an initial 7-day food record, and those with a BMI <18.5 kg/m^2 were excluded from the study. Additionally, pregnant or lactating women were not considered for participation.

Study Protocol

This randomized control parallel-arm study was conducted with college students enrolled at ASU. The primary outcome of the study was to examine the effects of a TRF protocol (i.e., an 18-hour fast) on diet quality (REAP-S questionnaire). Secondary outcomes examined were fasting resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures. Individuals interested in participating in the study completed an online pre-screening questionnaire to assess eligibility and were required to complete three in-person visits with the research team. Based on responses to the online screening survey, pre-qualified participants completed and returned a 7-day food log via email of all consumed foods and/or beverages, including meal-times, daily wake-times, and nightly bed-times. Individuals who completed a 7-day food record and who did not meet the exclusion criteria regarding typical fasting habits were invited to visit the research laboratory (Arizona Biomedical Collaborative building located at the ASU downtown Phoenix campus) for an in-person screening, written informed consent, and study enrollment.

In-person study visits were held by members of the research team, including a Registered Dietitian and trained research assistants. Each of the three required in-person visits lasted approximately one hour and required at least an 8-hour overnight fast (i.e., abstinence from all food and beverages except water). Further, women were scheduled to report for their in-person screening visit and to start the study within the first five days of menses. If participants presented to the screening visit in a fasted state, they completed a health questionnaire along with study outcomes, and this visit counted as the baseline visit (week 0). Conversely, participants who presented to the screening visit in an

unfasted state were scheduled for their baseline visit (week 0) at a future date. These participants were also given instructions to complete an overnight fast ahead of the visit.

At baseline (week 0) and week 4, participants received a 4-week fidelity calendar along with instructions to record compliance to the randomly assigned protocol, food and beverage intake throughout the day and night, daily meal-times, daily wake-time, and nightly bed-time. At baseline (week 0) and week 4, participants were also given a 4-day food log to record non-caloric and/or unsweetened beverages, and if necessary, any items consumed during the fasting window. Participants returned their first fidelity calendar and first 4-day food log at week 4 and their second fidelity calendar and second 4-day food log at week 8. All participants completed an exit survey (Appendix C) to assess satisfaction with the study and completed a data release form if they were interested in receiving their personal diet quality score and anthropometric measures (mean data). Following the study, participants were emailed an Amazon e-gift card ($25) to offset travel/parking. Finally, during each study visit, the research team utilized a data collection checklist (Appendix D) to ensure that all study activities (Appendix E) were completed.

Participants were matched on age, gender, weight, BMI, and exercise intensity (MET/min/wk). A coin flip was used to randomize paired participants into one of two groups: an 18-hour fast (INV) or 8-hour fast (CON). To minimize bias, research assistants obtaining anthropometric measures, and the research nurse and phlebotomist collecting blood samples were blinded to group allocation.

Intervention Arm. INV participants adhered to a daily 18-hour fasting protocol for 8 weeks. During the study, participants consumed foods and beverages of their choice

within one hour of waking and had a feeding window that extended 6 hours. Beyond the 6-hour mark, participants observed a prolonged fasting period (i.e., an 18-hour overnight fast). During fasting hours, participants were permitted to consume non-caloric beverages (preferably water but unsweetened and/or non-caloric coffee and tea were permitted). Participants did not receive diet instructions other than 'to fast' within the timeframe of the group they were randomized to. Participants were asked to maintain their typical physical activity patterns for the duration of the study. Additionally, participants self-elected one 'cheat-day' per week where they were excused from the fasting protocol. This 'cheat-day' (e.g., every Saturday) was held constant for the duration of the study.

Control Arm. Participants adhered to a daily 8-hour fasting protocol for 8 weeks. During the study, participants consumed foods and beverages of their choice within one hour of waking and had a feeding window that extended 16 hours. Beyond the 16-hour mark, participants observed a fasting period (i.e., an 8-hour overnight fast). During fasting hours, participants were permitted to consume non-caloric beverages (preferably water but unsweetened and/or non-caloric coffee and tea were permitted). Participants did not receive diet instructions other than 'to fast' within the timeframe of the group they were randomized to. Participants were asked to maintain their typical physical activity patterns for the duration of the study. Additionally, participants self-elected one 'cheat-day' per week where they were excused from the fasting protocol. This 'cheat-day' (e.g., every Saturday) was held constant for the duration of the study.

Outcome Measures

Diet Quality. Diet assessments were obtained by a registered dietitian at all study visits.

- ***A modified REAP-S questionnaire*** was completed for the previous week's intake at each study visit (Appendix F). The REAP-S questionnaire is a 16-item validated measure of diet quality with 13 scorable questions and three additional Likert scale questions.[116] Scores for REAP-S range from 13-39 points and higher scores are indicative of better diet quality. The REAP-S questionnaire estimates breakfast intake, dining out habits, whole grain, and high fiber starches, F&V, dairy, fat, animal protein, processed meats, fried foods, snack items, added fat, desserts, and sugar-sweetened beverages. Considering the study population (i.e., college students), the REAP-S questionnaire was modified by adding two additional questions that captured meals prepared from scratch and the reliance on frozen meals. Also, questions from the original REAP-S questionnaire with double negatives were modified for clarity. For the modified REAP-S questionnaire responses that covered 'poor diet quality attributes' were scored as follows: 'usually/often' with 1 point, 'sometimes' with 2 points, and 'rarely/never' or 'does not apply to me' with 3 points. Conversely, for questions covering 'good diet quality attributes' the scoring was reversed: 'usually/often' received 3 points, 'sometimes' received 2 points, and 'rarely/never' or 'does not apply to me' received 1 point. Collectively, all participants were scored on 15 questions (13 questions from the original REAP-S questionnaire and the 2 added questions which captured meals prepared from scratch and frozen meals). For the modified REAP-S questionnaire, possible scores ranged from 15-45, and higher scores were indicative of better diet quality.[256]

- ***A 24-hour dietary recall*** was obtained at each study visit. Participants were asked to report all foods and beverages consumed during the previous day, specifying what and how much they ate, and how their meals were prepared. A three-step multiple-pass interview method was used to collect data with different approaches for remembering foods: Quick List, Time and Occasion, and Detail passes. The timing of the dietary recall was such that it did not fall on a 'cheat day.'
- ***One 7-day food log*** was collected from participants during pre-screening. Data from this food log was used to examine additional markers of diet quality (i.e., total calories, dietary vitamin C, added sugars, and dietary saturated fat), and foods and beverages were entered into the Food Processor® Nutrition and Fitness Software (ESHA Research, Inc. Version 10.11, ©2012) for nutrient analysis.
- **Two *4-day food logs*** were collected from participants at week 4 and week 8. Food logs included all foods and beverages consumed during two weekdays, one weekend day, and the permitted 'cheat-day.' To examine additional markers of diet quality (i.e., total calories, dietary vitamin C, added sugars, and dietary saturated fat), foods and beverages from the 4-day food logs were entered into the Food Processor® Nutrition and Fitness Software for nutrient analysis.

Biomarkers. Fasting resting morning blood pressure and a blood draw to obtain fasting glucose, insulin, LDL cholesterol, triglycerides, and HDL cholesterol were obtained at all study visits. A single 30 mL fasting blood sample was acquired from participants' antecubital vein by a trained phlebotomist or a research nurse. Blood samples for glucose were collected into 2 ml gray top vacutainers, insulin was collected into serum tubes, and lipids were collected into EDTA vacutainers. Plasma was aliquoted to 0.5 ml with extra

serum and plasma stored for repeat analysis if needed. Prior to centrifugation, samples were stored in a preselected laboratory refrigerator. Centrifugation (at 3,000 RPM for 15 minutes) was used to separate plasma from whole blood within an hour of collection, and samples were labeled, dated, and stored at -80°C until needed for analysis.

- ***Fasting resting morning blood pressure*** was obtained prior to blood draw at all study visits. Participants were instructed to sit quietly with their feet planted flat on the floor. After a 10-minute rest period, a calibrated, non-invasive auto cuff blood (Omron® IntelliSense™ BP monitor Model: HEM-907XL) pressure monitor equipped with IntelliSense technology, which allows the machine to inflate and deflate at optimum levels depending on arm size, was utilized to obtain blood pressure in mm Hg. For this procedure, a blood pressure cuff was placed on participants' upper arm with the bottom end of the cuff positioned at approximately one inch above the antecubital fold. The cuff was inflated, and measurements were obtained three times; the mean of the second and third measurements was recorded. In the event of a machine malfunction that may introduce measurement errors, the research team was equipped to reset the blood pressure monitor to factory settings. Additionally, an identical model standby Omron blood pressure monitor was available for use. Fortunately, neither option was needed for the study. Based on findings from Johnston's laboratory, the mean coefficient of variation for the Omron blood pressure monitor was 3.9% for systolic and 3.4% for diastolic blood pressure, respectively.
- ***Fasting plasma glucose*** was measured using colorimetric enzymatic reagents on a bench-top, fully automated, clinical chemistry analyzer (Randox Daytona; Randox

Laboratories Ltd, Crumlin, UK). Sodium fluoride, a glycolysis inhibitor, was added to plasma prior to glucose measurements. Results were expressed in milligrams per deciliter (mg/dL).

- ***Fasting plasma insulin*** was measured using an ultrasensitive human radioimmunoassay kit (Millipore Corporation, Billerica, MA), and results were expressed in microunits per milliliter μU/mL. To limit antigen-binding sites, a fixed concentration of tracer antigen was incubated with antiserum, and the double antibody/PEG technique was used to measure the amount of tracer bound to the antibody.[257]
- ***HOMA-IR*** was calculated using the equation: HOMA-IR = glucose (mg/dL) x insulin ÷ 405).
- ***Fasting HDL cholesterol*** was measured using a commercially available diagnostic test kit on a bench-top, fully automated, clinical chemistry analyzer (Randox Daytona; Randox Laboratories Ltd, Crumlin, UK). HDL cholesterol was expressed in milligrams per deciliter (mg/dL).
- ***Fasting LDL cholesterol*** was calculated using the Friedewald equation: LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5. LDL cholesterol was expressed in milligrams per deciliter (mg/dL).[258]
- ***Fasting Triglycerides*** was measured using a commercially available diagnostic test kit on a bench-top, fully automated, clinical chemistry analyzer (Randox Daytona; Randox Laboratories Ltd, Crumlin, UK)., and results were expressed in milligrams per deciliter (mg/dL).

Anthropometric Measures and Physical Activity. Height was obtained at baseline (week 1). Weight, waist circumference, hip circumference, and MET were obtained at all study visits. All measures were obtained by a trained member of the research team.

- ***Height*** was obtained using a research-grade stadiometer (Cat. No. 2131821009, SECA 213, Birmingham, UK). Participants were instructed to stand without shoes and socks with their feet together and backs touching the measuring rod of the stadiometer. Participants were then instructed to stand upright in the Frankfurt line (i.e., with the corner of their eyes and top of their ears level) as their height was obtained. Measurements were taken to the nearest 0.5 centimeter and traditional rounding rules applied, when necessary.
- ***Weight*** was obtained using a calibrated total body composition analyzer (Cat. No. TBF-300, Tanita, Arlington Heights, IL) to the nearest 0.5 kg. Participants were instructed to empty their pockets and to remove socks and shoes, bulky clothing, and additional accessories. Participants stood upright with their hands at their side in the center of the scale's metal platform.
- ***Waist circumference*** was obtained to the nearest 0.5 cm using a research-grade ergonomic measuring tape placed horizontally around participants' natural waist (i.e., narrowest circumference above the umbilicus). Waist circumference was measured twice and averaged unless the difference between the first and second measurement was greater than 0.5 cm. In that event, a third measurement was obtained, and the mean of the nearest two circumferences was recorded.
- ***Hip circumference*** was obtained to the nearest 0.5 cm using a research-grade ergonomic measuring tape placed horizontally around participants' widest portion of

the posterior. Hip circumference was measured twice and averaged unless the difference between the first and second measurement was greater than 0.5 cm. In that event, a third measurement was obtained, and the mean of the nearest two circumferences was recorded.

- ***MET*** was calculated using the validated Godin-Shephard Leisure-time Physical Activity Questionnaire.[259] This three-item questionnaire estimates weekly participation in 'light, 'moderate,' and 'vigorous' activities. Scores ≥24 are considered 'active,' and those ≤23 indicate 'insufficient activity.'[260] MET is recorded in min/wk.

Sample Size Calculation

An a priori sample size calculation was conducted using an alpha level of 0.05 with 80% power, and effect sizes for diet quality (i.e., REAP-S score) and cardiometabolic outcomes (i.e., blood pressure, fasting blood glucose, fasting insulin, LDL cholesterol, triglycerides, and HDL cholesterol) (Appendix G). The median sample size ranged from 15 per group (actual) to 28 per group (calculated). Based on calculated figure, and to ascertain an adequate sample size to detect statistically significant changes, the targeted sample size, per group, accounting for a 20% attrition was 34.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) v.25 was utilized for all computations. Baseline characteristics (i.e., age, BMI, and MET) were presented using descriptive statistics. Data are reported as mean ± standard deviation. A repeated measures ANOVA test was utilized to assess the time x group effects of the CON vs.

INV group on outcome measures (i.e., diet quality, resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures and physical activity). However, as a result of missing blood data, and self-report of survey data and anthropometric measures due to COVID-19 restrictions, a non-parametric Mann Whitney U test was used to compare the between-group change from baseline to week 4 for all outcome measures. These statistics were used to test all hypotheses. P-values are two-tailed, and statistical significance was assumed at p-values < 0.05.

Given that the present study was underpowered (51% powered based on the degree of change and the SD for diet quality), effect sizes accompanied p-values to explain the overall magnitude of effect for all outcome measures. The partial eta squared was calculated to indicate effect size for the repeated measures ANOVA. Partial eta squared effect sizes from 0.06-0.13 are considered 'medium' and effect sizes >0.13 are considered 'large'.[261] An r (correlation coefficient) value (r = z score ÷ square root of N where N is equal to the total number of cases) was used to determine effect sizes based on the non-parametric Mann Whitney U test.[262] Once calculated, the r correlation coefficient was compared to Cohen's 1988 effect size standard, which specifies 0.1 as a "small" effect, 0.3 as a "medium" effect, and ≥ 0.5 as a "large" effect.[262,263]

Potential confounding variables were identified during primary analyses. Specifically, at baseline, there was an imbalance between the CON and INV groups for age ($p = 0.043$). However, when entered as a covariate, age did not impact the outcome measures between the groups (i.e., diet quality and body weight). Next, a non-parametric technique was used to handle outliers. Inherent to its design, the Mann Whitney U test

ranks data, thereby representing the relative position of data points. Indeed, when compared to parametric techniques, the Mann Whitney U test is not sensitive to outliers, which can impact analysis outcomes of parametric statistical tests. To address the issue of non-compliance due to COVID-19, an intent-to-treat analysis was used. This conservative procedure presents a “real life” scenario and is less likely to infer that the intervention is effective compared to other analyses (i.e., as-treated analysis or per-protocol analysis). Hence, the last observation carried forward (LOCF) method was used to impute missing values for week 8 data.

CHAPTER 4

RESULTS

Subject Characteristics

The initial online screening survey yielded 216 responses. Of these, 45 volunteers met the inclusion criteria and were invited to complete a 7-day food record before the first in-person study visit. Twenty-nine individuals (93% women) returned their 7-day food record and were randomized into the study: 13 participants were allocated to the CON group (92% women), and 16 participants were allocated to the INV group (93% women). Before the week 4 data collection, 3 participants from the CON group and 8 participants from the INV group withdrew from the study. Between weeks 4 and 8, one INV participant withdrew from the study (Figure 1). Thus, 17 participants completed the study in its entirety (10 CON [77%] and 7 INV [44%]; $p = 0.154$).

Due to COVID-19, in-person visits ceased before all participants completed the 8-week data collection. Hence, week 4 data were carried forward to week 8 for seven participants (last observation carried forward (LOCF) method), including the one participant who withdrew from the trial between weeks 4 and 8. For one of the participants carried forward, the blood sample collected at week 4 was insufficient for all analyses. Hence, data for 18 participants are presented in the final analyses (10 CON, 8 INV) with the exception of analyses for insulin and blood lipids where the total samples are 10 CON and 7 INV. Also carried forward were data for REAP-S (1 INV), dietary data (1 INV), and compliance data (2 CON and 1 INV).

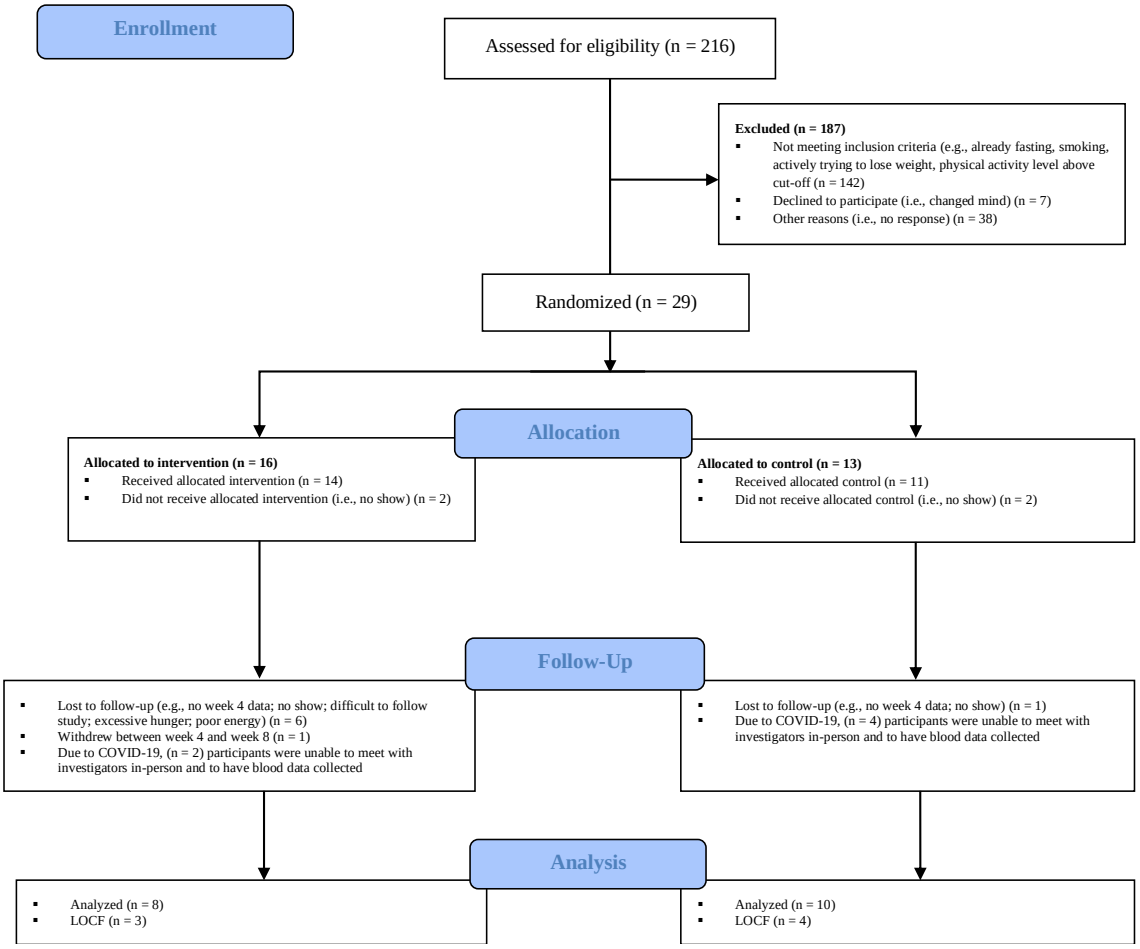

Figure 1. Consort Flow Diagram

Due to one missing data point, compliance data are reported for 10 CON and 7 INV. Compliance to the study protocol was self-reported using fidelity calendars from week 0 (baseline) to week 4 and from week 4 to week 8. From week 0 to week 4, self-reported compliance was 97% for the CON group and 91% for the INV group. From week 4 to week 8, self-reported compliance was 95% and 87% for the CON and INV group, respectively. There were no significant differences in compliance by group ($p = 0.193$). Calculated compliance did not align with self-reported compliance for the CON group at week 4. Indeed, at week 4, CON participants self-reported that their mean nightly fast was 8 hours; however, the calculated mean nighty fast for the CON group

was 12 hours at week 4 (CON = 0% compliance). Conversely, at week 4, the average self-reported and calculated nightly fast for the INV group was 18 hours (INV = 71% compliance; 29% fasted for approximately 19 hours per night). At week 0 (baseline), the mean fasting time for the CON group and INV group was 12 hours. These data indicate that the CON group maintained their mean baseline fasting length, whereas the INV group changed their mean fasting length during the study.

As outlined in Table 1, age differed between the CON and INV groups at baseline ($p = 0.043$); however, when entered as a covariate, age did not impact the outcome measures that displayed significant time x group interactions (i.e., diet quality and body weight). There were no significant differences between groups for BMI and MET at baseline ($p = 0.146$ and $p = 0.146$, respectively).

Table 1. Subject Characteristics at Baseline

Baseline	N	Mean	Standard Deviation	P-value
Gender				
CON	M 1, F 9			0.357
INV	F 8			
Age (years)				
CON	10	21.8	3.8	0.043*
INV	8	25.1	4.1	
BMI (kg/m^2)				
CON	10	24.3	2.4	0.146
INV	8	22.2	2.2	
MET (min/wk)				
CON	10	68.7	41.3	0.146
INV	8	46.8	24.4	

Descriptive statistics were performed with SPSS Statistical Analysis System (version 23.0) using nonparametric analyses (Mann-Whitney U test). Data are presented as mean and standard deviation, and findings are considered statistically significant at p-value < 0.05.

Diet Quality

REAP-S Score. It was hypothesized that, following the 8-week study, participants randomized to the INV group (i.e., the 18-hour fasting regimen) would have improvements in diet quality scores (measured by REAP-S) compared to participants randomized to the CON group (i.e., the 8-hour fasting regimen). As shown in Table 2, a repeated measures ANOVA test showed no significant difference in REAP-S scores between groups from baseline, week 4, and week 8 ($p = 0.239$, effect size was large = 0.174). Similarly, as shown in Table 3, change in REAP-S score between groups did not differ significantly at week 4 and week 8 vs. baseline ($p = 0.139$, effect size was large = 0.132). However, as depicted in Figure 2, the Mann-Whitney U test showed a significant improvement in REAP-S score from baseline to week 4 for the INV group vs. the CON group ($p = 0.030$). Change in REAP-S was not correlated with change in other outcome measures ($p > 0.05$).

Table 2. REAP-S Score between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
REAP-S	CON	10	35.6 ± 2.8	34.3 ± 3.4	35.0 ± 3.1	0.239	0.174
	INV	8	37.7 ± 2.8	38.5 ± 3.3	37.7 ± 2.6		

Repeated measures ANOVA used to compare REAP-S score between groups at baseline, week 4, and week 8. REAP-S score represented as mean ± standard deviation.

Table 3. Change in REAP-S Score between Groups

			Time			
Outcome	**Group**	**N**	**Week 4**	**Week 8**	**P-value**	**Effect Size**
Δ	CON	10	-1.3 ± 3.4	-0.6 ± 2.8	0.139	0.132
REAP-S	INV	8	0.7 ± 1.1	0.0 ± 1.7		

Repeated measures ANOVA used to compare change (Δ) in REAP-S score at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). REAP-S score represented as mean ± standard deviation.

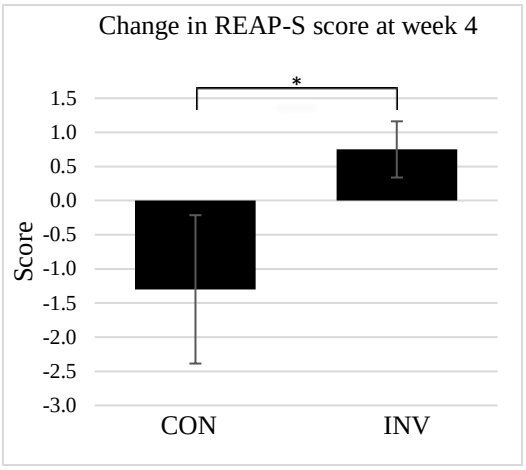

Figure 2. Change in REAP-S Score between Groups from Baseline to Week 4. The Mann-Whitney U test used to compare the change in REAP-S score between groups at baseline and week 4. * indicates a significant improvement in REAP-S score from baseline to week 4 for the INV group vs. the CON group; p = 0.030; *r* effect size = 0.511 (large magnitude of effect).

Total Calories, Dietary Vitamin C, Added Sugars, and Dietary Saturated Fat.

As shown in Table 4, there were no significant differences between groups for total calories, dietary vitamin C, and added sugars (p = 0.778, effect size = 0.035; p = 0.420, effect size = 0.117; and p = 0.391, effect size = 0.125 for total calories, vitamin C, and added sugars, respectively). Interestingly, there was a significant decrease in dietary saturated fat for the CON group compared to the INV group (p = 0.044, effect size was large = 0.359) from baseline, week 4, and week 8.

In Table 5, change in total calories, dietary vitamin C, added sugars, and dietary saturated fat between groups did not differ significantly at week 4 and week 8 vs. baseline (p = 0.552, effect size = 0.024; p = 0.180, effect size = 0.117; p = 0.633, effect size = 0.016; and p = 0.433, effect size = 0.041 for total calories, vitamin C, added sugars, and saturated fat, respectively). As depicted in Figures 3, 4, and 5, the Mann-Whitney U test showed no significant differences in total calories, dietary vitamin C, and added sugars from baseline to week 4 (p = 0.435, p = 0.696, and p = 0.845 for total

calories, vitamin C, and added sugars, respectively). As shown in Figure 6, there was a trend for change in saturated fat to differ between groups from baseline to week 4 ($p = 0.064$).

Table 4. Total Calories, Dietary Vitamin C, Added Sugars, and Dietary Saturated Fat between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
Total Calories (kcal)	CON	10	1920 ± 412	1901 ± 488	1839 ± 503	0.778	0.035
	INV	7	2029 ± 431	1750 ± 469	1879 ± 441		
Vitamin C (mg)	CON	10	60.8 ± 26.2	47.8 ± 20.9	62.2 ± 29.6	0.420	0.117
	INV	7	90.6 ± 62.6	81.6 ± 56.8	76.6 ± 51.6		
Added Sugars (g)	CON	10	7.2 ± 6.1	14.2 ± 29.3	19.5 ± 18.1	0.391	0.125
	INV	7	11.3 ± 11.1	12.6 ± 12.2	13.1 ± 11.3		
Saturated Fat (%)	CON	10	11.6 ± 2.6	9.9 ± 3.4	11.1 ± 2.8	0.044*	0.359
	INV	7	13.5 ± 8.2	17.6 ± 13.0	17.5 ± 11.1		

Repeated measures ANOVA used to compare total calories, dietary vitamin C, added sugars, and dietary saturated fat between groups at baseline, week 4, and week 8. Data are represented as mean ± standard deviation. * indicates a significant change between groups.

Table 5. Change in Total Calories, Dietary Vitamin C, Added Sugars, and Dietary Saturated Fat between Groups over Time

			Time			
Outcome	Group	N	Week 4	Week 8	P-value	Effect Size
Δ Total Calories (kcal)	CON	10	-18.4 ± 816.9	-80.2 ± 685.5	0.552	0.024
	INV	7	-278.9 ± 686.9	-150.3 ± 643.6		
Δ Vitamin C (mg)	CON	10	-12.6 ± 33.9	1.7 ± 42.2	0.180	0.117
	INV	7	-8.3 ± 53.9	-13.3 ± 54.7		
Δ Added Sugars (g)	CON	10	7.0 ± 28.4	12.2 ± 16.9	0.633	0.016
	INV	7	1.3 ± 10.2	1.8 ± 12.8		
Δ Saturated Fat (%)	CON	10	-1.7 ± 4.7	-0.5 ± 3.0	0.433	0.041
	INV	7	4.1 ± 5.3	4.0 ± 3.5		

Repeated measures ANOVA used to compare change (Δ) in total calories, dietary vitamin C, added sugars, and dietary saturated fat at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). Total calories, vitamin C, added sugars, and saturated fat represented as mean ± standard deviation.

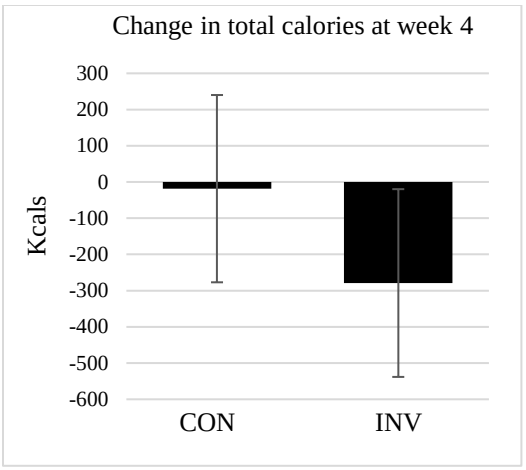

Figure 3. Change in Total Calories between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in total calories (kcal) between groups at baseline and week 4; p = 0.435; *r* effect size = 0.189 (small magnitude of effect).

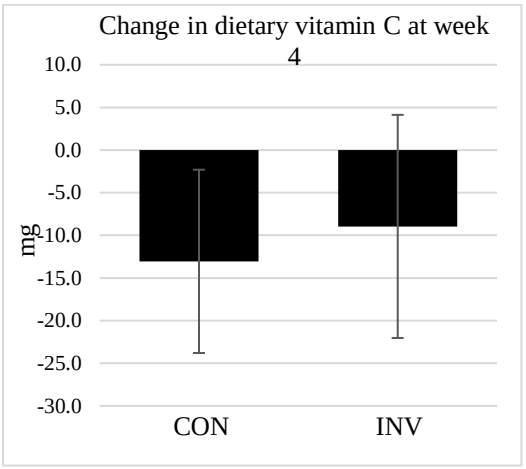

Figure 4. Change in Dietary Vitamin C between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in vitamin C (mg) between groups at baseline and week 4; p = 0.696; *r* effect size = 0.094 (small magnitude of effect).

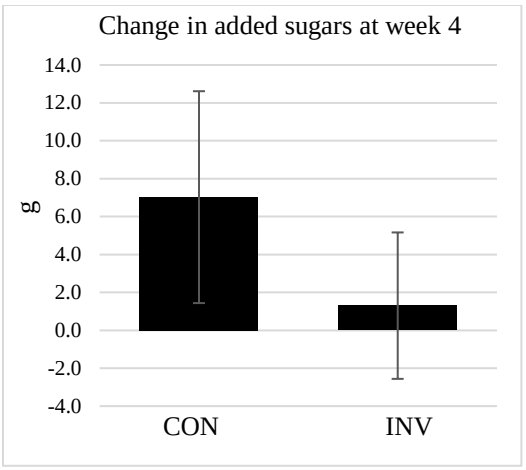

Figure 5. Change in Added Sugars between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in added sugars (g) between groups at baseline and week 4; p = 0.845; *r* effect size = 0.047 (small magnitude of effect).

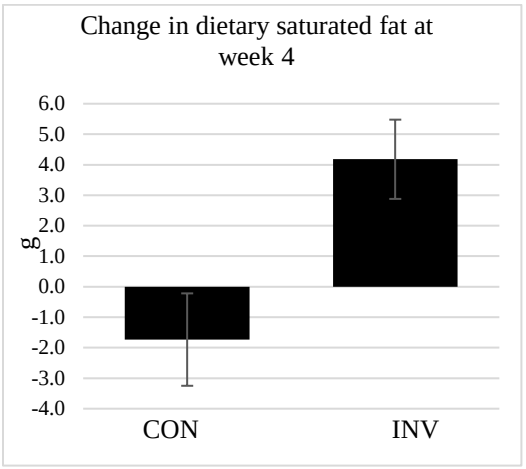

Figure 6. Change in Dietary Saturated Fat between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in saturated fat (%) between groups at baseline and week 4. Dietary saturated fat tended to increase from baseline to week 4 for the INV group vs. the CON group; p = 0.064; *r* effect size = 0.449 (medium magnitude of effect).

Resting Morning Blood Pressure

It was hypothesized that, following the 8-week study, participants randomized to the INV group would have improvements in resting morning blood pressure (measured by Omron auto cuff blood pressure monitor) compared to participants randomized to the CON group. As depicted in Table 6, a repeated measures ANOVA test showed no

significant difference in resting morning systolic or diastolic blood pressure between groups from baseline, week 4, and week 8 ($p = 0.521$, effect size = 0.083 and $p = 0.674$, effect size = 0.051 for systolic and diastolic blood pressure, respectively).

Similarly, as shown in Table 7, change in resting morning systolic or diastolic blood pressure between groups did not differ significantly at week 4 and week 8 vs. baseline ($p = 0.407$, effect size = 0.043 and $p = 0.397$, effect size = 0.045 for change in resting morning systolic and diastolic pressure, respectively). Finally, as depicted in Figures 7 and 8, the Mann-Whitney U test showed no significant improvement in resting morning systolic or diastolic blood pressure between groups from baseline to week 4 ($p = 0.423$ and $p = 0.929$ for resting morning systolic and diastolic blood pressure, respectively).

Table 6. Resting Morning Blood Pressure between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
Systolic BP (mm Hg)	CON	10	111.1 ± 12.0	110.4 ± 9.5	110.9 ± 8.5	0.521	0.083
	INV	8	108.6 ± 11.2	101.8 ± 15.4	106.7 ± 10.7		
Diastolic BP (mm Hg)	CON	10	69.6 ± 9.1	70.0 ± 8.5	68.2 ± 10.6	0.674	0.051
	INV	8	68.6 ± 10.5	66.7 ± 11.5	67.4 ± 9.1		

Repeated measures ANOVA used to compare resting morning blood pressure between groups at baseline, week 4, and week 8. Data are represented as mean ± standard deviation.

Table 7. Change in Resting Morning Blood Pressure between Groups

			Time			
Outcome	**Group**	**N**	**Week 4**	**Week 8**	**P-value**	**Effect Size**
Δ Systolic BP (mm Hg)	CON	10	-0.7 ± 5.9	-0.2 ± 5.6	0.407	0.043
	INV	8	-6.9 ± 15.7	-1.9 ± 6.0		
Δ Diastolic BP (mm Hg)	CON	10	0.5 ± 3.7	-1.4 ± 5.5	0.397	0.045
	INV	8	-1.9 ± 9.8	-1.2 ± 8.1		

Repeated measures ANOVA used to compare change (Δ) in resting morning blood pressure between groups at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). Data are represented as mean ± standard deviation.

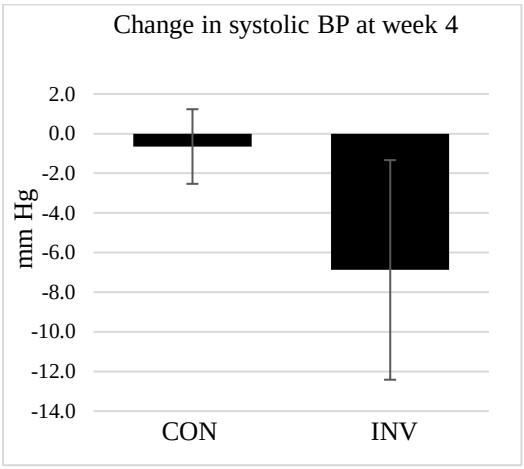

Figure 7. Change in Resting Systolic BP between Groups from Baseline to Week 4. The Mann-Whitney U test was used to compare the change in resting morning systolic BP (mm Hg) between groups at baseline and week 4; p = 0.423; *r* effect size = 0.188 (small magnitude of effect).

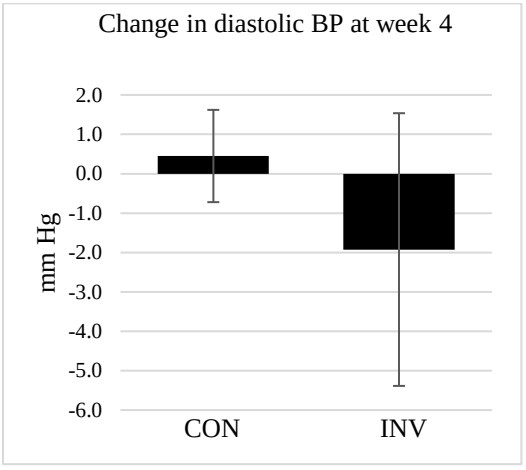

Figure 8. Change in Resting Diastolic BP between Groups from Baseline to Week 4. The Mann-Whitney U test was used to compare the change in resting morning diastolic BP (mm Hg) between groups at baseline and week 4; p = 0.929; *r* effect size = 0.020 (small magnitude of effect).

Biomarkers of Glucose Regulation

It was hypothesized that, following the 8-week study, participants randomized to the INV group would have lower biomarkers of glucose regulation (i.e., fasting glucose and insulin) compared to participants randomized to the CON group. As depicted in Table 8, a repeated measures ANOVA test showed no significant differences between

groups for fasting glucose and fasting insulin from baseline, week 4, and week 8 (p = 0.183, effect size was large = 0.203; and p = 0.985, effect size = 0.002 for fasting glucose and insulin, respectively. Table 8 also shows no significant differences between groups for Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) (p = 0.832, effect size = 0.026).

Similarly, as shown in Table 9, change in fasting blood glucose, insulin, and HOMA-IR between groups did not differ significantly at week 4 and week 8 vs. baseline (p = 0.163, effect size = 0.118; p = 0.953, effect size = 0.000; and p = 0.807, effect size = 0.004 for fasting blood glucose, insulin, and HOMA-IR, respectively). Figure 9 shows that there was a trend for change in fasting glucose to differ between groups from baseline to week 4 (p = 0.091). Conversely, change in insulin and HOMA-IR did not differ between groups from baseline to week 4 (p = 0.696, Figure 10 for insulin; and p = 0.380, Figure 11 for HOMA-IR).

Table 8. Fasting Blood Glucose, Insulin, and HOMA-IR between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
Blood glucose (mg/dL)	CON INV	10 8	97.6 ± 6.4 95.3 ± 7.0	99.0 ± 5.8 90.5 ± 5.7	97.4 ± 5.8 92.8 ± 5.1	0.183	0.203
Insulin (µU/mL)	CON INV	10 7	11.9 ± 3.5 8.7 ± 3.1	12.2 ± 3.9 8.9 ± 2.5	11.1 ± 4.8 7.7 ± 2.1	0.985	0.002
HOMA-IR	CON INV	10 7	2.8 ± 0.9 2.1 ± 0.8	3.0 ± 0.9 2.0 ± 0.6	2.6 ± 1.1 1.7 ± 0.5	0.832	0.026

Repeated measures ANOVA used to compare fasting blood glucose and insulin between groups at baseline, week 4, and week 8. Data are represented as mean ± standard deviation.

Table 9. Change in Fasting Blood Glucose, Insulin, and HOMA-IR between Groups

			Time			
Outcome	**Group**	**N**	**Week 4**	**Week 8**	**P-value**	**Effect Size**
Δ Blood glucose (mg/dL)	CON INV	10 8	1.3 ± 4.0 -4.7 ± 8.8	-0.2 ± 4.2 -2.4 ± 7.2	0.163	0.118
Δ Insulin (µU/mL)	CON INV	10 7	0.3 ± 2.7 0.1 ± 2.0	-0.8 ± 3.2 -1.0 ± 2.8	0.953	0.000
Δ HOMA-IR	CON INV	10 7	0.1 ± 0.6 -0.1 ± 0.7	-0.2 ± 0.8 -0.3 ± 0.8	0.807	0.004

Repeated measures ANOVA used to compare change (Δ) in fasting blood glucose and insulin between groups at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). Data are represented as mean ± standard deviation.

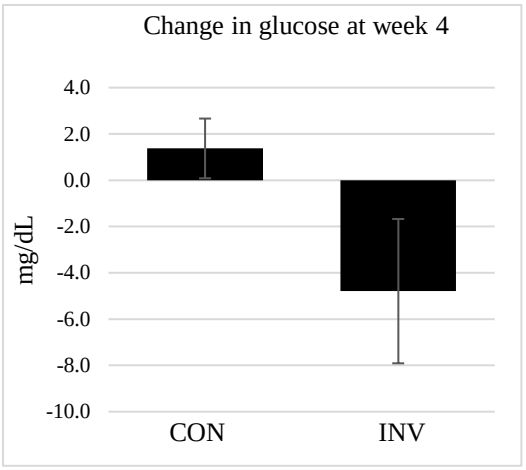

Figure 9. Change in Fasting Blood Glucose between Groups from Baseline to Week 4. The Mann-Whitney U test was used to compare the change in fasting blood glucose (mg/dL) between groups at baseline and week 4. Fasting blood glucose tended to improve from baseline to week 4 for the INV group vs. the CON group; p = 0.091; *r* effect size = 0.397 (medium magnitude of effect).

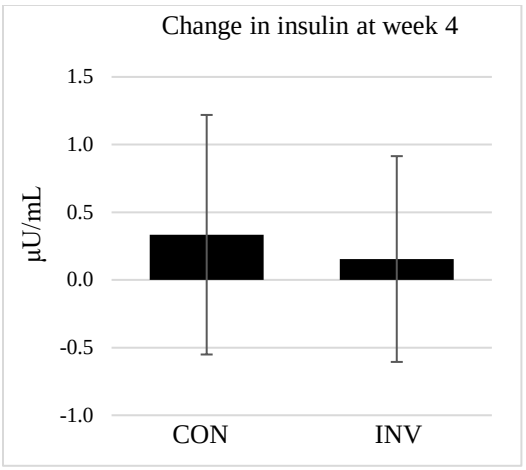

Figure 10. Change in Insulin between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in fasting insulin (µU/mL) between groups at baseline and week 4; p = 0.696; *r* effect size = 0.094 (small magnitude of effect).

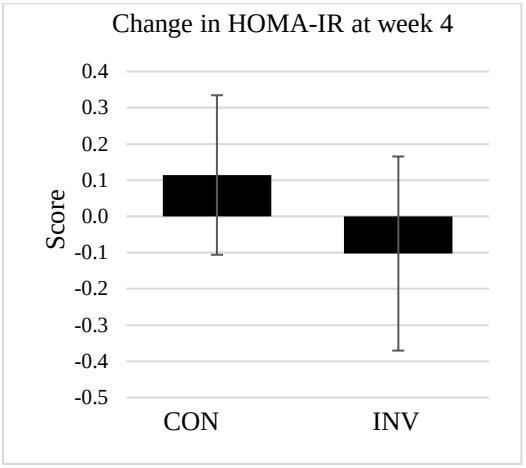

Figure 11. Change in HOMA-IR between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in HOMA-IR between groups at baseline and week 4; p = 0.380; *r* effect size = 0.213 (small magnitude of effect).

Biomarkers of Lipid Metabolism

It was hypothesized that, following the 8-week study, participants randomized to the INV group would have improvements in biomarkers of lipid metabolism (i.e., LDL cholesterol, triglycerides, and HDL cholesterol) compared to participants randomized to the CON group. As depicted in Table 10, a repeated measures ANOVA test showed no significant difference in LDL cholesterol, triglycerides, or HDL cholesterol between

groups from baseline, week 4, and week 8 (p = 0.495, effect size = 0.096; p = 0.936, effect size = 0.009; and p = 0.567, effect size = 0.078 for LDL cholesterol, triglycerides, and HDL cholesterol, respectively).

Similarly, as shown in Table 11, change in LDL cholesterol, triglycerides, or HDL cholesterol between groups did not differ significantly at week 4 and week 8 vs. baseline (p = 0.869, effect size = 0.002; p = 0.822, effect size = 0.003; and p = 0.667, effect size = 0.013 for change in LDL cholesterol, triglycerides, and HDL cholesterol, respectively). Finally, as illustrated in Figures 12, 13, and 14, the Mann-Whitney U test showed no significant differences between groups for LDL cholesterol, triglycerides, or HDL cholesterol from baseline to week 4 (p = 0.494, p = 1.000, and p = 0.354 for LDL cholesterol, triglycerides, and HDL cholesterol, respectively).

Table 10. LDL Cholesterol, Triglycerides, and HDL Cholesterol between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
LDL (mg/dL)	CON	10	108.8 ± 20.7	108.9 ± 23.0	108.1 ± 20.5	0.495	0.096
	INV	7	101.2 ± 27.3	93.7 ± 19.8	92.2 ± 26.8		
TG (mg/dL)	CON	10	68.9 ± 25.7	74.0 ± 42.1	72.4 ± 44.3	0.936	0.009
	INV	7	61.1 ± 19.1	61.2 ± 26.4	61.4 ± 25.7		
HDL (mg/dL)	CON	10	60.0 ± 9.6	61.0 ± 12.3	62.1 ± 13.2	0.567	0.078
	INV	7	63.7 ± 14.7	61.0 ± 10.4	63.2 ± 14.7		

Repeated measures ANOVA used to compare LDL cholesterol, triglycerides, and HDL cholesterol between groups at baseline, week 4, and week 8. Data are represented as mean ± standard deviation.

Table 11. Change in LDL Cholesterol, Triglycerides, and HDL Cholesterol between Groups

			Time			
Outcome	**Group**	**N**	**Week 4**	**Week 8**	**P-value**	**Effect Size**
Δ LDL (mg/dL)	CON	10	-0.1 ± 10.7	-0.7 ± 9.5	0.869	0.002
	INV	7	-7.4 ± 14.8	-9.0 ± 20.1		
Δ TG (mg/dL)	CON	10	5.0 ± 27.1	3.4 ± 26.2	0.822	0.003
	INV	7	0.1 ± 27.4	0.3 ± 20.1		
Δ HDL (mg/dL)	CON	10	1.0 ± 6.6	2.1 ± 7.1	0.667	0.013
	INV	7	-2.6 ± 8.2	-0.5 ± 10.7		

Repeated measures ANOVA used to compare change (Δ) in LDL cholesterol, triglycerides, and HDL cholesterol between groups at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). Data are represented as mean ± standard deviation.

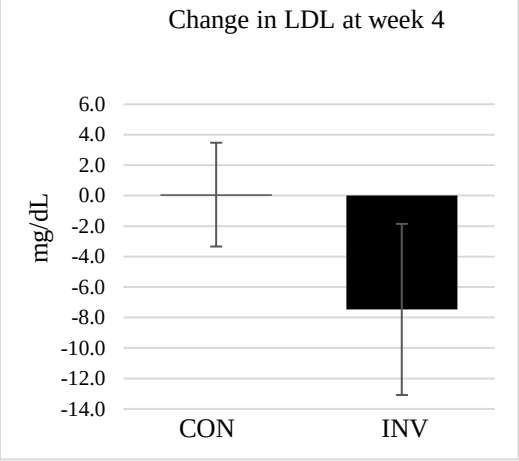

Figure 12. Change in LDL Cholesterol between Groups from Baseline to Week 4. The Mann-Whitney U test was used to compare the change in LDL cholesterol (mg/dL) between groups at baseline and week 4; p = 0.494; *r* effect size = 0.165 (small magnitude of effect).

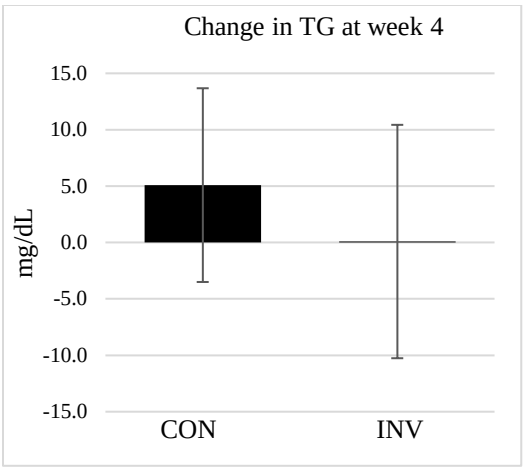

Figure 13. Change in TG between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in TG (mg/dL) between groups at baseline and week 4; p = 1.000; *r* effect size = 0.00 (no effect).

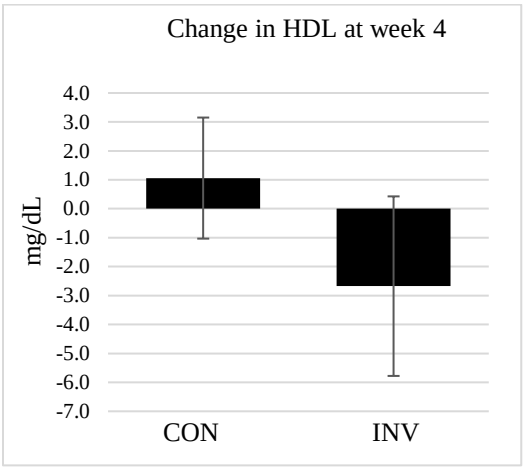

Figure 14. Change in HDL Cholesterol between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in HDL cholesterol (mg/dL) between groups at baseline and week 4; p = 0.354; *r* effect size = 0.224 (small magnitude of effect).

Anthropometric Measures and Physical Activity

It was hypothesized that, following the 8-week study, participants randomized to the INV group would have improvements in anthropometric measures (i.e., body weight, waist circumference, and hip circumference) compared to participants randomized to the CON group. As shown in Table 12, a repeated measures ANOVA test showed a trend toward differences for weight between groups from baseline, week 4, and week 8 (p =

0.071, effect size was large = 0.297). Conversely, there were no significant differences in waist circumference or hip circumference between groups from baseline, week 4, and week 8 ($p = 0.445$, effect size = 0.102; and $p = 0.388$, effect size = 0.119 for waist circumference, and hip circumference, respectively). Also shown in Table 12, there were no significant differences for MET between groups from baseline, week 4, and week 8 ($p = 0.621$, effect size = 0.061).

Next, as seen in Table 13, change in weight, waist circumference, hip circumference, and MET between groups did not differ significantly at week 4 and week 8 vs. baseline ($p = 0.937$, effect size = 0.000; $p = 0.337$, effect size = 0.058; $p = 0.280$, effect size = 0.072; and $p = 0.322$, effect size = 0.061 for weight, waist circumference, hip circumference, and MET, respectively). However, the Mann-Whitney U test showed a significant reduction in body weight and a trend for reduction in hip circumference for the INV group from baseline to week 4 ($p = 0.016$, Figure 15 for body weight; and $p = 0.100$, Figure 16 for hip circumference). Conversely, as shown in Figures 17 and 18, there were no significant differences between groups for waist circumference or MET from baseline to week 4 ($p = 0.450$ and $p = 0.534$ for waist circumference and MET, respectively).

Table 12. Weight, Waist Circumference, Hip Circumference, and MET between Groups over Time

Outcome	Group	N	Week 0 (Baseline)	Week 4	Week 8	P-value	Effect Size
Weight (kg)	CON	10	67.6 ± 10.5	68.3 ± 11.3	68.1 ± 11.0	0.071	0.297
	INV	8	59.4 ± 6.3	58.4 ± 6.3	58.2 ± 5.6		
Waist (cm)	CON	10	75.7 ± 6.9	76.0 ± 7.6	71.2 ± 13.8	0.445	0.102
	INV	8	69.4 ± 4.7	68.5 ± 3.9	69.8 ± 5.6		
Hip (cm)	CON	10	101.1 ± 7.0	100.7 ± 7.8	92.7 ± 18.6	0.388	0.119
	INV	8	95.7 ± 6.6	94.1 ± 4.9	95.2 ± 9.7		
MET (min/wk)	CON	10	68.7 ± 41.3	63.4 ± 36.3	64.4 ± 35.6	0.621	0.061
	INV	8	46.8 ± 24.4	51.2 ± 37.2	43.6 ± 35.1		

Repeated measures ANOVA used to compare weight, waist circumference, hip circumference, and MET between groups at baseline, week 4, and week 8. Data are represented as mean ± standard deviation.

Table 13. Change in Weight, Waist Circumference, Hip Circumference, and MET between Groups

			Time			
Outcome	**Group**	**N**	**Week 4**	**Week 8**	**P-value**	**Effect Size**
Δ Weight (kg)	CON	10	0.6 ± 1.3	0.4 ± 1.6	0.937	0.000
	INV	8	-1.1 ± 1.6	-1.2 ± 2.6		
Δ Waist (cm)	CON	10	0.3 ± 2.2	-4.4 ± 17.0	0.337	0.058
	INV	8	-0.9 ± 3.2	0.3 ± 3.7		
Δ Hip (cm)	CON	10	-0.4 ± 1.3	-8.4 ± 21.7	0.280	0.072
	INV	8	-1.6 ± 3.0	-0.5 ± 7.0		
Δ MET (min/wk)	CON	10	-5.3 ± 20.4	-4.3 ± 16.5	0.322	0.061
	INV	8	4.3 ± 30.8	-3.2 ± 17.5		

Repeated measures ANOVA used to compare change (Δ) in weight, waist circumference, hip circumference, and MET between groups at week 4 (week 4 value minus baseline value) and at week 8 (week 8 value minus baseline value). Data are represented as mean ± standard deviation.

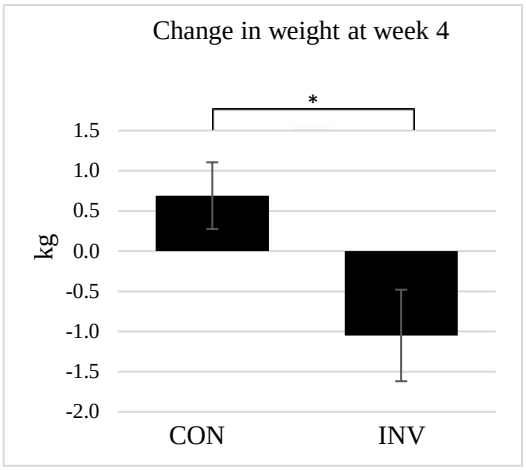

Figure 15. Change in Weight between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in body weight (kg) between groups at baseline and week 4. * indicates a significant decrease in weight from baseline to week 4 for the INV group vs. the CON group; p = 0.016; *r* effect size = 0.566 (large magnitude of effect).

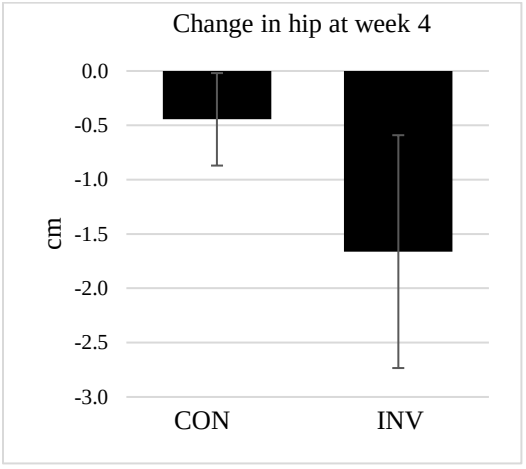

Figure 16. Change in Hip Circumference between Groups from Baseline to week 4.
The Mann-Whitney U test was used to compare the change in hip circumference (cm) between groups at baseline and week 4. Hip circumference tended to improve from baseline to week 4 for the INV group vs. the CON group; p = 0.100; *r* effect size = 0.387 (medium magnitude of effect).

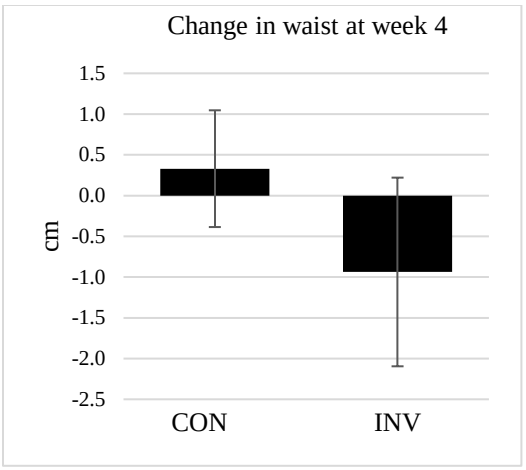

Figure 17. Change in Waist Circumference between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in waist circumference (cm) between groups at baseline and week 4; p = 0.450; *r* effect size = 0.178 (small magnitude of effect).

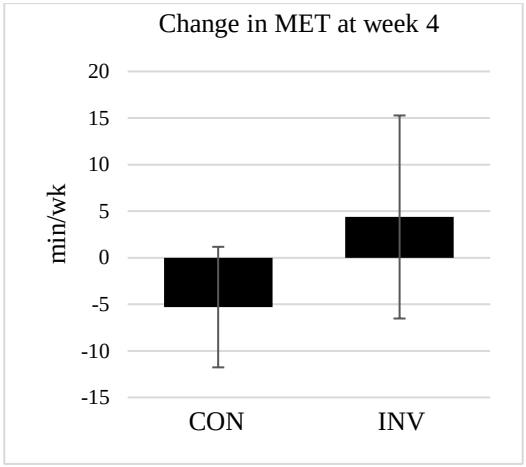

Figure 18. Change in MET between Groups from Baseline to Week 4.
The Mann-Whitney U test was used to compare the change in MET (min/wk) between groups at baseline and week 4; p = 0.534; *r* effect size = 0.146 (small magnitude of effect).

CHAPTER 5

DISCUSSION

The primary objective of this 8-week randomized parallel-arm study was to examine the effects of an 18-hour TRF protocol vs. an 8-hour TRF fast on diet quality. Diet quality was measured with the REAP-S questionnaire. Secondary outcomes were resting morning blood pressure, biomarkers of glucose regulation, biomarkers of lipid metabolism, and anthropometric measures. It was hypothesized that participants randomized to the INV group would have improvements in all outcome measures. Due to COVID-19 restrictions, several participants were prohibited from meeting with the research team for their final in-person appointment. As such, blood data were not collected for these participants. Further, the research team relied on participants' self-report for survey data and anthropometric measures. As a result of missing data and self-reports for select outcomes at week 8, week 8 data will not be discussed; however, these data are reported in chapter 4. Additionally, at week 4, the calculated nightly fast for the CON group was 12 hours, whereas the calculated nightly fast for the INV group was 18 hours. It is important to note that, for the CON group, the nightly fasting duration did not change from baseline. For the purposes of this discussion, the non-parametric Mann Whitney U was used to assess statistically significant differences between the INV and CON group at week 4 (i.e., week 4 minus baseline). Additionally, given that the present study is underpowered (i.e., 51% powered), *r* (correlation coefficient) effect sizes (i.e., *r* = *z* score ÷ square root of N. N is equal to the total number of cases) will accompany p-values to explain the overall magnitude of effect for all outcome measures. An *r* effect size is used for the non-parametric Mann Whitney U test, and once calculated, is

compared to Cohen's 1988 standard which specifies that effect sizes of 0.1 = "small", 0.3 = "medium", and ≥ 0.5 = "large".[262,263]

Previous TRF studies have also been underpowered; therefore, although there was a significant difference between the groups for change in diet quality (in favor of the INV group), the level of confidence in these data could not be determined as the investigators were unable to conduct appropriate sensitivity analyses.

Diet Quality

REAP-S Score. The hypothesis that diet quality (i.e., REAP-S score) would improve following the intervention was supported. In other words, the TRF intervention had an effect on diet quality that appeared to favor the INV vs. the CON group. Specifically, diet quality increased by a mean of 0.7 points for the INV group, while the CON group had a mean decrease of 1.3 points from baseline to week 4.

Since this is the first known trial to assess the effects of a TRF protocol on diet quality (as assessed by REAP-S), future studies are needed before conclusions can be made. However, as with other diet quality indices (e.g., HEI-2010), a higher REAP-S score is indicative of better diet quality. According to findings from the NIH-AARP Diet and Heathy Study (n = 492,823 with a 15-year follow-up) which examined the relationship between four diet quality indices and all-cause mortality, CVD mortality, and cancer mortality, higher diet quality scores were associated with greater reduction in risk for mortality from all causes, CVD, and cancer.[264] Next, according to Cox proportional-hazard models for cause-specific and total mortality among women in the Nurses' Health Study (n = 47, 994) and men in the Health Professionals Follow-up Study (n = 25,745), pooled hazard ratios for all-cause mortality were 0.91 for the A-HEI score, 0.84 for the

Alternate Mediterranean Diet Score, and 0.89 for the DASH score for participants with the greatest improvements in diet quality (i.e., 13-33% improvement) compared to participants with stable diet quality over a 12-year period.[124] Further, the authors indicated that a 20% increase in diet quality score was consistently associated with an 8-17% reduction in the risk for total mortality, and a 7-15% reduction in risk for CVD-related mortality.[124]

Higher diet quality has also been associated with a reduced risk for overweight and obesity. For example, women in the Framingham Offspring and Spouse Study (n = 590; normal weight) with lower diet quality were more likely to develop overweight or obesity compared to women with higher diet quality over a 16-year period. Indeed, the authors reported that after adjustment for age, activity level, and smoking status, women with lower diet quality had 1.76 higher odds of becoming overweight or obese compared to women with higher diet quality.[265]

In the present study, an examination of individual REAP-S questions revealed that breakfast consumption improved for both the INV and CON group; however, savory snacks decreased for the INV group while the CON group decreased fruit intake from baseline to week 4. These findings may explain the improvements in diet quality for the INV group. Further, the average overall REAP-S score for participants in this study is comparable to that of participants in a previously published secondary data analysis (Appendix H) which validated the REAP-S questionnaire against the HEI-2010 for select biomarkers of health including BMI, blood pressure, fasting plasma glucose, triglyceride, and nutrient intakes.[116] Interestingly, when compared to the HEI-2010, only the REAP-S

was significantly correlated with vitamin C, another indicator of diet quality (Johnston, 2018).

Total Calories, Dietary Vitamin C, Added Sugars, and Dietary Saturated Fat. Along with REAP-S, data on total calories, vitamin C, added sugars, and saturated fat were also obtained. For total calories, there was a 279 kcal non-significant mean decrease for the INV group and an 18 kcal non-significant mean decrease for the CON group. For dietary vitamin C, there was an 8.3 mg non-significant mean decrease for the INV group and a 12.6 mg non-significant mean decrease for the CON group. For added sugars, there was a 1.3 g non-significant mean increase for the INV group and a 7.0 g non-significant mean increase for the CON group.

Lack of statistical findings for total calories, dietary vitamin C, and added sugars for the INV group may be explained by participants' baseline values of these outcomes. Indeed, when compared to current recommendations (Appendix H), participants in the INV group met or exceeded recommendations for dietary vitamin C and added sugars and were just below the recommendation for total calories. Therefore, it is unlikely that significant improvements would be seen for these outcomes. Collectively, managing caloric intake, consuming adequate amounts of vitamin C, and limiting added sugars are associated with a more healthful dietary pattern (DGA 2015-2020); therefore, these data suggest that participants in this study had relatively healthful baseline eating patterns. Future research should include participants with less healthful baseline eating patterns to determine if the TRF intervention results in a greater increase in diet quality score.

Compared to total calories, dietary vitamin C, and added sugars, there was a trend toward statistical significance for saturated fat from baseline to week 4 ($p = 0.064$).

Specifically, there was a 4.1 g mean increase for the INV group and a 1.7 g mean decrease for the CON group. While an increase in dietary saturated fat was unexpected since saturated fat is typically inversely associated with diet quality and risk for CVD,[266,267] a trend in saturated fat increase may potentially be explained by the INV group's increased consumption in breakfast as well as their response to the REAP-S question: *In the past week, how often did you add butter or margarine to bread, potatoes, rice or vegetables at the table?*. Indeed, from baseline to week 4, the INV group reported an increase in butter or margarine consumption, which may have accompanied their increase in breakfast consumption during that time period. It is also important to note that, at baseline, both groups were above the percent recommendations for dietary saturated fat; however, at week 4, only the INV group was above the percent recommendation for dietary saturated fat.

While the REAP-S questionnaire does not differentiate between butter or margarine consumption, it is important to note that butter, an animal fat, is higher in saturated fat while margarine, a plant fat, has little to no saturated fat. Instead, margarine typically consumes higher amounts of mono- and poly-unsaturated fats, which may be associated with higher diet quality.[268] In a nationally representative sample (n = 4,751 men, n = 4,572 women, and n = 4,939 boys and girls between 2-19 years old), participants who consumed peanuts, which is higher in mono- and poly-unsaturated fats, had better diet quality (based on HEI-2010) compared to non-peanut consumers.[269] Interestingly, improvements in diet quality were seen despite that saturated fat consumption was similar between groups for men, women, and girls. Additionally, findings from a meta-analysis of prospective studies (n = 21 studies with 347,747

subjects during a 5-23-year follow-up period) showed no significant evidence that dietary saturated fat is associated with an increased risk for CVD.[270] These findings were in contrast with a recently published meta-analysis of prospective studies (n = 29 studies with 1,148,117 participants), which reported a significant association between dietary saturated fat and mortality from coronary heart disease. Despite these contrasting findings, dietary saturated fat alone may not be indicative of overall diet quality and health, thereby highlighting the importance of viewing eating patterns from a more global perspective.[271]

Resting Morning Blood Pressure

The hypothesis that resting morning blood pressure would improve following the intervention was not supported. However, for systolic blood pressure, there was a 6.9 mm Hg non-significant mean decrease for the INV group and a 0.7 mm Hg non-significant mean decrease for the CON group. For diastolic blood pressure, there was a 1.9 mm Hg non-significant mean decrease for the INV group and a 0.5 mm Hg non-significant mean increase for the CON group.

Results from the present study align with some, but not all, previous research findings. Indeed, four recent studies showed no significant improvements in blood pressure following an IF intervention.[272–275] Conversely, other researchers have reported a significant decrease in blood pressure,[27,276–278] and one known study has reported an increase in blood pressure in participants. In the study that reported an increase in blood pressure, the authors indicated that differences in values might have occurred because of a time-of-day effect, where, for the intervention group, blood pressure was obtained in the late afternoon whereas participants in the control group had their blood pressure taken

in the early morning.[23] This explanation supports the claim that blood pressure follows a 24-hour circadian rhythm in which values are lower during sleep and in the early morning and higher during the day and into the afternoon.[279]Lack of statistical findings for the INV group may be explained by participants' normal baseline values for systolic and diastolic blood pressure. Therefore, it is unlikely that significant improvements would have been seen for systolic and diastolic blood pressure.

Biomarkers of Glucose Regulation

The hypothesis that biomarkers of glucose regulation (i.e., fasting blood glucose, and insulin) would improve following the intervention was not supported. However, there was a trend for change in blood glucose between the groups from baseline to week 4 ($p = 0.091$). Specifically, there was a 4.7 mg/dL mean decrease for the INV group and a 1.3 mg/dL mean increase for the CON group. For insulin, there was a 0.1 μU/mL non-significant mean increase for the INV group and a 0.3 μU/mL non-significant mean increase for the CON group from baseline to week 4. Along with fasting blood glucose and insulin, HOMA-IR was also calculated using the equation: HOMA-IR = glucose (mg/dL) x insulin ÷ 405). There was a 0.1 non-significant mean decrease for the INV group and a 0.1 non-significant mean increase for the CON group.

Results from the present study align with some, but not all, previous research findings. Indeed, some authors have reported no improvements in fasting glucose[272–277] while others have either found statistically significant improvements[26,280–282] or a trend toward significant improvements for fasting glucose.[283] When examining the studies without significant improvements, most participants had a baseline fasting glucose within normal ranges (< 100 mg/dL). In the one pilot study conducted on participants with

baseline fasting glucose levels above the normal ranges (105.6 mg/dL), there was a non-significant increase following the TRF intervention. In the studies that showed significant improvement or a trend for improvement in fasting blood glucose, the subject pool included participants with overweight and obesity and those at risk for T2DM. A recently published systematic review and meta-analysis suggest that the glucoregulatory benefits of TRF may be limited to individuals with metabolic abnormalities.[284]

As with fasting blood glucose, research is divided on the effects of TRF on insulin. Where some authors reported significant improvements[26,27] or a trend toward significant improvements,[283] other authors reported no difference in insulin following a TRF intervention.[273,274,280,281] Mixed findings were also observed for HOMA-IR. Indeed, following their 8-week study examining the effects of a TRF protocol on weight and metabolic risk factors in participants with obesity, the authors found no statistically significant differences for HOMA-IR between the INV and CON groups.[277] Participants' normal baseline HOMA-IR values may explain why the authors did not see an improvement in the study sample. Conversely, following their 4-day randomized crossover TRF trial, the authors reported a significant improvement in HOMA-IR. The significant reduction in fasting blood glucose and insulin could explain the significant improvement in HOMA-IR in the INV group.[282]

Lack of statistical findings for fasting glucose in the INV group may be explained by participants' normal baseline values. Additionally, since baseline values for insulin were within normal ranges, it was unlikely that HOMA-IR would improve for the INV group. Further, a closer examination indicated that participants in the present study did not meet the criteria for metabolic syndrome (participants had two or fewer criteria).[285]

Next, when examining participants with sub-optimal fasting blood glucose (i.e., >100 mg/dL; 2 INV), the TRF protocol had no favorable metabolic benefits.

Biomarkers of Lipid Metabolism

The hypothesis that biomarkers of lipid metabolism (i.e., LDL cholesterol, triglycerides, and HDL cholesterol) would improve following the intervention was not supported. However, for LDL cholesterol, there was a 7.4 mg/dL non-significant mean decrease for the INV group and a 0.1 mg/dL non-significant mean decrease for the CON group. For triglycerides, there was a 0.1 mg/dL non-significant mean increase for the INV group and a 5.0 mg/dL non-significant mean increase for the CON group. For HDL cholesterol, there was a 2.3 mg/dL non-significant mean decrease for the INV group and a 1.0 mg/dL non-significant mean increase for the CON group.

Results from the present study align with some, but not all, previous research findings. Most studies examining the effects of TRF on LDL cholesterol have shown no significant differences[26,27,273,274,277,280,286,287] while two studies have shown that levels of LDL cholesterol increase following a TRF intervention.[23,272] In the studies with increased levels of LDL cholesterol, participants were allowed to eat later in the day (between 7 PM – 9 PM)[23,272] which may explain the increase in levels. Indeed, for every 100 calories consumed at night, there was associated with a 1.08 mg/dL increase in levels of LDL cholesterol.[274] While no known TRF study has shown statistically significant improvements in LDL cholesterol, a recent study reported a trend toward improvements for levels of LDL cholesterol in patients with MetS.[283]

Significant improvements in triglycerides have been reported in four known TRF studies[23,26,274,286] with a subject pool that included healthy participants, resistant-trained

men, and patients with non-alcoholic fatty liver disease. Conversely, one known study has found an increase in triglycerides following their TRF study. The authors contend that the elevation in triglycerides may have occurred as a result of the re-esterification of triglycerides following lipolysis due to the 18-hour TRF protocol.[27] As with LDL cholesterol, most studies examining the effects of TRF on HDL cholesterol have shown no significant differences[26,27,272–274,277,280,286,287] while two studies have shown increases in levels of HDL cholesterol following a TRF intervention.[23,286] Conversely, one known TRF study has shown a reduction in HDL cholesterol.

Lack of statistical findings for LDL cholesterol in the INV group aligns with the majority of previous research. Next, participants' baseline values of triglycerides and HDL cholesterol were within normal reference ranges, which suggests that, overall, participants did not have issues with lipid metabolism. Based on these data, it is unlikely that significant improvements would be seen for biomarkers of lipid metabolism.

Anthropometric Measures and Physical Activity

The hypothesis that anthropometric measures (i.e., body weight, waist circumference, and hip circumference) would improve following the intervention was partially supported. For weight, there was a significant difference between the INV and CON group from baseline to week 4. Specifically, body weight decreased by a mean of 1.1 kg for the INV group, while the CON group had a mean increase of 0.6 kg from baseline to week 4. For waist circumference, there was a -0.9 cm non-significant mean decrease for the INV group and a 0.3 cm non-significant mean increase for the CON group. For hip circumference, there was a trend toward statistical significance ($p = 0.100$). Specifically, there was a 1.6 cm mean decrease for the INV group and a 0.4 cm mean decrease for the

CON group. Along with body weight, waist circumference, and hip circumference, data on MET was also obtained. Specifically, there was a 4.3 min/wk non-significant mean increase for the INV group and a 5.3 min/wk non-significant mean decrease for the CON group.

Results from the present study align with some, but not all, previous research findings. While some researchers have reported no statistically significant differences in weight following a TRF protocol,[27,210,280] there have been reports of significant differences in weight in numerous other studies.[25,28,274,277,281,283,288] Fewer TRF studies have addressed waist circumference, and no known studies have examined the impact of TRF on hip circumference or MET. Of the three studies examining waist circumference, one showed a significant reduction,[283] another showed no difference,[274] and the final study showed a significant increase in waist circumference.[289] An increase in waist circumference was seen in an examination of an early-TRF (one meal consumed between 8 AM – 9:30 AM) vs. a late-TRP protocol (one meal consumed between 8 PM – 9:30 PM. While no control group was included in this study, the authors credited the increase in waist circumference to the late-TRF group.[289]

Statistically significant reduction in weight (a 1.1 kg loss) seen in the INV group from baseline to week 4 may be explained by the daily reduction in calories (i.e., 279 less calories per day). However, a closer look at % body fat calculations revealed no statistically significant differences between the groups ($p = 0.762$). These data suggest that weight loss was not attributed to a reduction in % body fat. Hence, it could be that water weight was responsible for the reduction in body weight. Lack of statistical

findings for waist circumference, hip circumference, and MET may be explained by participants' optimal baseline values for these outcomes.

Popular dietary interventions typically report weight loss; however, many of these regimens credit the reduction in body weight to caloric restriction.[290] Due to the nature of these diets, it is often difficult for individuals to sustain weight loss especially once caloric intake in increased. Next, since food is responsible for approximately 20% of water intake,[291] and fasting individuals tend to eat less, in the present study, reduction in weight was likely due to fluctuations in water weight. However, even if the weight loss was attributed to a reduction in % body fat, it is highly questionable if the TRF protocol could be sustained over time (43% attrition rate in the present study). While no known studies have examined TRF for an extended number of years, weight re-gain appears to be common occurrence in other dietary interventions that restrict caloric intake. Therefore, the feasibility of current findings is questionable especially in light of participants' comments regarding the intervention. For example, one participant remarked that *"it was difficult to eat all my food in such a short window",* while another mentioned that *"it was hard to have dinner with family and friends because my dinner was earlier than usual."*

Strengths

This randomized control study had several notable strengths. First, this is the first known study to utilize a TRF protocol to influence diet quality in college students. Next, considering that the investigators did not prescribe a specific eating pattern, participants were free to eat ad libitum provided that eating was restricted to the specified eating window. This approach may have revealed a natural shift in dietary choices, including a

reduction in snacks in the INV group. Another strength of the present study is that participants were granted a "cheat" day each week. This allowed participants to increase their eating window, as desired, for one day each week. Other strengths are that participants were asked to maintain their exercise habits and to refrain from caffeine prior to their in-person visits. Research suggests that change in exercise habits can impact the outcome variables and that caffeine consumption may interfere with blood pressure readings.

Limitations

There are limitations to the present study. First, a reverse power analysis indicated that the study was 51% powered. In other words, there was only a 51% probability that the study would detect a treatment difference between the INV and CON group for diet quality. Next, due to COVID-19 restrictions, several participants were unable to meet with investigators for the final 8-week visit to obtain anthropometric measurements and blood data. As a result of these restrictions, week 8 data were not as robust as originally planned. Therefore, reliance was placed on the Mann-Whitney U test for statistical analyses of the change data between baseline and week 4. Additionally, participants enrolled in the present study were predominantly healthy, which may partially explain why select outcome measures showed no significant improvements. As such, it may be prudent for future studies to recruit participants at greater risk for cardiometabolic conditions. Additionally, given that the present study was underpowered, it is difficult to interpret effect sizes;[292] therefore, future research is needed in this area. Finally, although there was a significant difference between the groups for change in diet quality (in favor

of the INV group), the level of confidence in these data could not be determined as the investigators were unable to conduct appropriate sensitivity analyses.

Conclusion

Findings from the present study suggest that a daily 18-hour TRF protocol may be effective for improving diet quality in college students attending ASU. Additionally, the TRF protocol was effective for reducing body weight; however, these data should be interpreted with caution as weight loss seen in the present study may be the result of water weight. An unexpected finding from the present study is that dietary saturated fat increased for the INV group from baseline to week 4. The rise in dietary saturated fat may be the result of increased butter consumption during the breakfast meal. Further research, including studies with additional study populations, larger sample sizes, and longer durations, are needed to determine if currents findings hold true and are generalizable to larger populations.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

ASU Knowledge Enterprise Development

APPROVAL: MODIFICATION

Carol Johnston
CHS: Health Solutions, College of
602/496-2539
CAROL.JOHNSTON@asu.edu

Dear Carol Johnston:

On 10/25/2019 the ASU IRB reviewed the following protocol:

Type of Review:	Modification/Update
Title:	Mealtime Matters: An 8-wk Randomized-Controlled Trial to Examine the Effects of a Daily Time-Restricted Feeding Protocol on Diet Quality
Investigator:	Carol Johnston
IRB ID:	STUDY00010810
Funding:	Name: Graduate College
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• protocol , Category: IRB Protocol; • health questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Food log, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • consent, Category: Consent Form;

The IRB approved the modification.

When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

APPENDIX B

CONSENT FORM

Informed Consent

Fasting and Health in College Students

INTRODUCTION

The purposes of this form are (1) to provide you with information that may affect your decision as to whether or not to participate in this research study, and (2) to record your consent if you choose to be involved in this study.

RESEARCHERS

Dr. Carol Johnston (ASU Nutrition professor) and Selicia Mayra (registered dietitian and ASU doctoral student in nutrition), have requested your participation in a research study.

STUDY PURPOSE

The purpose of this study is to investigate the effects of fasting on health including common blood biomarkers, disposition, and anthropometrics in college students.

DESCRIPTION OF RESEARCH STUDY

You have indicated to us that you are a non-smoker and ≥18 years of age and healthy. You have not recently dieted for weight loss, regularly fast ≥12 hours per day, followed fasting regimens (i.e., alternate day fasting, Ramadan-style fasting, 5:2 fasting), and if female, you are not currently pregnant or planning a pregnancy, and you either have a regular cycle or are currently on hormonal contraceptives (i.e., birth control pills, IUDs, or patches). Also, you are not currently ill or taking prescription medications for a medical condition, and you do not work the night shift. You will be randomly assigned to a fasting arm of the study: the 18-hour fast or the 8-hour fast. You are asked to follow the fasting protocol 6 days a week for 8 weeks. You will select one day of the week (e.g., Friday or Saturday) as 'cheat day' for the entire study and on this day you do not need to 'fast'. You may eat the foods of your choice during the study, and we ask that you maintain your normal physical activities and not initiate a new exercise protocol.

This research entails three study visits to our test facilities on ASU's Downtown Phoenix campus for up to 60 minutes per session. You will be asked to complete diet recalls and mood/cognitive questionnaires and your height, body weight, blood pressure, and waist and hip circumference will be measured, and a small amount of blood (<2 tablespoons) will be collected from an arm vein during these three visits. No food or beverage aside from water is to be consumed for the 8 hours prior to this blood draw. Blood will be used to measure biomarkers related to cardiovascular health such as cholesterol and ketones. You will receive a $25 e-gift card to Amazon once you have completed your final visit to our test facilities.

RISKS

You may feel hungry and unfocused during the fasting periods; you are allowed to consume unsweetened and non-caloric beverages such as water, coffee and tea during

this period. The blood draw will be performed by trained staff (either a registered nurse or a registered radiology technician) under sterile conditions. You may feel lightheaded or nauseous when your blood is drawn and you may bruise; our staff are trained to handle such situations. You may feel discomfort when blood pressure is recorded due to the cuff constriction.

BENEFITS
You may not benefit from this study, but once the study is complete you will be provided with your data, if desired. You will need to complete a study release form to receive your test results.

NEW INFORMATION
If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

CONFIDENTIALITY
All information obtained in this study is strictly confidential unless disclosure is required by law. The results of this research study may be used in reports, presentations, and publications, but your name or identity will not be revealed. In order to maintain confidentiality of your records, Dr. Johnston will use subject codes on all data collected, maintain a master list separate and secure from all data collected, and limit access to all confidential information to the study investigators.

WITHDRAWAL PRIVILEGE
You may withdraw from the study at any time for any reason without penalty or prejudice toward you. Your decision will not affect you any manner. We ask that you notify us in a timely manner if you decide to withdraw from the study, and we will ask you to complete the exit survey at that time.

COSTS AND PAYMENTS
You will receive a $25 Amazon e-gift card for participation in this trial. There are no payments required for this study; however, you may need to pay for curbside parking at the test site (rate: $1.50/hour).

COMPENSATION FOR ILLNESS AND INJURY
If you agree to participate in the study, then your consent does not waive any of your legal rights. However, in the event of harm, injury, or illness arising from this study, neither Arizona State University nor the researchers are able to give you any money, insurance coverage, free medical care, or any compensation for such injury. Major injury is not likely but if necessary, a call to 911 will be placed.

VOLUNTARY CONSENT
Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by Dr. Carol Johnston, 550 N. 3rd St., Phoenix, AZ 85004. [602-496-2539]

Institutional Review Board, through the ASU Research Compliance Office, at 480-965 6788.

This form explains the nature, demands, benefits and any risk of the project. By signing this form you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given to you.

Your signature below indicates that you consent to participate in the above study.

_____	_____	_____
Subject's Signature	Printed Name	Date
_____	_____	
Contact Phone Number	Email	

INVESTIGATOR'S STATEMENT

"I certify that I have explained to the above individual the nature and purpose, the potential benefits, and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Human Research Protections to protect the rights of human subjects. I have provided the subject/participant a copy of this signed consent document."

Signature of Investigator _____ Date _____

APPENDIX C

EXIT SURVEY

Exit Survey Date: _____ PID#: _____

1. Did you have difficulties sticking to the fasting protocol for the entire study? Y N
   If yes, please explain: _____
   _____

2. On a scale of 1 (lowest) to 5 (highest), how hungry did you feel when you first started the study?

3. Did your hunger decrease (get better) the longer you were on the fasting protocol? Y N

4. What did you like best about the fasting protocol?
   Explain: _____
   _____

5. Do you have any comments or concerns that you would like to share with the researchers? Y N
   If yes, please indicate here: _____
   _____
   _____

APPENDIX D

DATA COLLECTION CHECKLIST

Data Collection Checklist Visit#: _____ Date: _____ PID#: _____

- ☐ Consent + participant copy
- ☐ Recruitment flyer
- ☐ Research results acknowledgement statement
- ☐ Health questionnaire
- ☐ WHOQOL-BREF
- ☐ Happiness scale
- ☐ Blood pressure
- ☐ 24-hour dietary recall guide
- ☐ Diet questionnaire
- ☐ Fidelity calendar
- ☐ Future visits scheduled
- ☐ 4-day food log packet and instructions

- ☐ Stroop test
- ☐ Trail making test part A
- ☐ Trail making test part B

- ☐ Profile of mood states
- ☐ GAD-7 scale
- ☐ Height
- ☐ Weight
- ☐ Waist
- ☐ Hip

- ☐ Blood draw

- ☐ Exit survey (at final visit only)

APPENDIX E

STUDY ACTIVITIES

Item	Study Visit 1 Baseline (week 0)	Study Visit 2 (week 4)	Study Visit 3 (week 8)
Screening			
Health Questionnaire	✓		
Compliance			
Fidelity Calendar		✓	✓
Diet Quality			
24-hour Dietary Recall	✓	✓	✓
REAP-S Questionnaire	✓	✓	✓
4-day Food Log		✓	✓
Resting Morning Blood Pressure			
Fasting Systolic Blood Pressure	✓	✓	✓
Fasting Diastolic Blood Pressure	✓	✓	✓
Biomarkers of Glucose Regulation			
Fasting Glucose	✓	✓	✓
Fasting Insulin	✓	✓	✓
HOMA-IR	✓	✓	✓
Biomarkers of Lipid Metabolism			
LDL Cholesterol	✓	✓	✓
Triglycerides	✓	✓	✓
HDL Cholesterol	✓	✓	✓
Anthropometric Measures and Physical Activity			
Height	✓		
Weight	✓	✓	✓
Waist circumference	✓	✓	✓
Hip circumference	✓	✓	✓
MET	✓	✓	✓

APPENDIX F

MODIFIED REAP-S QUESTIONNAIRE

Diet Questionnaire Visit#: ____ Date: _____ PID#:_____

In an average week, how often do you:	Usually/ Often	Sometimes	Rarely/Never	
1. Skip breakfast?	○	○	○	
2. Eat 4 or more meals from sit-down or take out restaurants?	○	○	○	
3. Eat 2 or more servings of whole grain products or high fiber starches a day? Serving = 1 slice of 100% whole grain bread; 1 cup whole grain cereal like Shredded Wheat, 3-4 whole grain crackers, ½ cup brown rice or whole wheat pasta, boiled or baked potatoes, yuca, yams or plantain.	○	○	○	*
4. Eat 2 or more servings of fruit a day? Serving = ½ cup or 1 med. fruit or ¾ cup 100% fruit juice.	○	○	○	*
5. Eat 2 or more servings of vegetables a day? Serving = ½ cup vegetables, or 1 cup leafy raw	○	○	○	*
6. Eat or drink 2 or more servings of milk, yogurt, or cheese a day? Serving = 1 cup milk or yogurt; 1½ - 2 ounces cheese.	○	○	○	I follow a vegan * diet ○
7. Eat more than 2 servings (see sizes below) of meat, chicken, turkey or fish per day? Serving=3 ounces of meat or chicken (the size of a deck of cards) (e.g., 1 regular hamburger, 1 chicken breast or leg [thigh and drumstick], or 1 pork chop)	○	○	○	I follow a vegetarian/vegan diet ○
8. Use processed meats (like bologna, salami, corned beef, hotdogs, sausage or bacon) instead of low fat processed meats (like roast beef, turkey, lean ham; low-fat cold cuts/hotdogs)?	○	○	○	I follow a vegetarian/vegan diet ○
9. Eat fried foods (such as French fries, fried plantains, tostones, fried yucca, fried chicken, or fried fish)?	○	○	○	
10. Eat regular potato chips, nacho chips, corn chips, crackers, regular popcorn?	○	○	○	
11. Add butter or margarine to bread, potatoes, rice or vegetables at the table?	○	○	○	
12. Eat sweets like cake, cookies, pastries, donuts, muffins, chocolate and candies more than once per day.	○	○	○	
13. Drink 16 ounces or more of non-diet soda, fruit drink/punch or Kool-Aid a day? Note: 1 can of soda = 12 ounces	○	○	○	
14. Prepare your meals from scratch as opposed to eating take-out, prepared, or convenience meals?	○	○	○	*
15. Eat processed foods such as frozen pizza and microwaveable dinners?	○	○	○	

16. Eat or drink 2 or more servings of dairy-free milk, yogurt, or cheese a day?	○	○	○	*
17. Eat 2 or more servings of meat-alternatives such as vegetable burgers, tofu, seitan, or tempeh a day?	○	○	○	

APPENDIX G

SAMPLE SIZE CALCULATION

Outcome Variable	Pre-Post	SD	Effect Size	n (per group)	Calculated Sample Size (per group)	Source	Year
REAP-S (diet quality score)*	35.3-39.8	1.75	3 *estimate*	15,18	14	Mayra	2019
Systolic BP (mm Hg)	128-121	14.38	7	23	68	Gabel	2018
Diastolic BP (mm Hg)	82.9-74.5	10.8	8.4	15	27	Eshghinia	2013
Fasting Glucose (mg/dL)	102-96	11.79	6	15	62	Eshghinia	2013
Fasting Insulin μU/mL	8.3-5.7	3.35	2.6	23	28	Gabel	2018
LDL (mg/dL)	116.8-103.4	8.9	10.5	10	13	Johnson	2006
HDL (mg/dL)	44.0-48.1	1.3	4.1	10	3	Johnson	2006
Triglycerides (mg/dL)	160.5-143.9	22.77	16.6	15	31	Eshghinia	2013
				Mean: 16 Median: 15	Mean: 31 Median 28		

*Data from a cross-sectional study. The effect size of 3 represents improvement in 3 of 16 questions (this measure has not been used in an intervention study to date).

APPENDIX H

REFERENCE RANGES FOR OUTCOME MEASURES

Outcome	Group	Baseline (mean)	Week 4 Value (mean)	Difference at Week 4 (mean)	Previous Data/ Dietary Recommendation	Source
REAP-S (score)	CON INV	35.6 37.7	34.3 38.5	-1.3 0.7	36	Johnston, 2018[116]
Total Calories (kcal)	CON INV	1,920 2,029	1,901 1,750	-18 -279	2,000-2,400	DGA 2015-2020[293]
Vitamin C (mg)	CON INV	60.8 90.6	47.8 81.6	-12.6 -8.3	75	DGA 2015-2020[293]
Added Sugars (%)	CON INV	1.5 2.3	2.9 2.8	2.5 0.6	<10	DGA 2015-2020[293]
Saturated Fat (%)	CON INV	11.6 13.5	9.9 17.6	1.7 4.1	<10	DGA 2015-2020[293]
Systolic BP (mm Hg)	CON INV	111.1 108.6	110.4 101.8	-0.7 -6.9	<120	AHA, 2020[294]
Diastolic BP (mm Hg)	CON INV	69.6 68.6	70.0 66.7	0.5 -1.9	<80	AHA, 2020[294]
Fasting Blood Glucose (mg/dL)	CON INV	97.6 95.3	99.0 90.5	1.3 -4.7	<100	ADA[295]
Fasting Insulin (μU/mL)	CON INV	11.9 8.7	12.2 8.9	0.3 0.1	< 25	Buppajarntham, 2015[296]
HOMA-IR	CON INV	2.8 2.1	3.0 2.0	0.1 -0.1	<0.5-1.4	Blood Code, 2016[297]
LDL (mg/dL)	CON INV	108.8 101.2	108.9 93.7	-0.1 -7.4	<100	LDL MedlinePlus, 2017[298]
TG (mg/dL)	CON INV	68.9 61.1	74.0 61.2	5.0 0.1	<150	TG MedlinePlus[299]
HDL (mg/dL)	CON INV	60.0 63.7	61.0 61.0	1.0 -2.6	>40 (men) >50 (women)	HDL MedlinePlus[300]
Weight (kg)	CON INV	67.6 59.4	68.3 58.4	0.6 -1.1	-	-
Waist (cm)	CON INV	75.7 69.4	76.0 68.5	0.3 -0.9	<102 (men) <88 (women)	McGee, 2016[301]
Hip (cm)	CON INV	101.1 95.7	100.7 94.1	-0.4 -1.6	94-105 (men) 97-108 (women)	Molarius, 1999[302]
MET (min/wk)	CON INV	68.7 46.8	63.4 51.2	-5.3 4.3	≥24 (active) ≤23 (insufficiently active)	Amireault, 2015[260]