UNIVERSITY OF CALIFORNIA SAN DIEGO

Effects of Time-restricted Eating on Weight and Body Composition in Adults with Metabolic Syndrome

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by

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The thesis of Aryana Pazargadi is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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ABSTRACT OF THE THESIS

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Professor Britta Larsen, Chair

Metabolic syndrome (MetS) is a pathologic condition characterized by a cluster of risk factors, such as high blood pressure, high blood sugar levels, an increased body mass index (BMI), and abnormal cholesterol levels, all of which raise the risk of cardiovascular disease and

type 2 diabetes. MetS affects a large proportion of the United States population, especially those over the age of 60. Time-restricted eating (TRE), which entails limiting one's daily eating window to 10 hours or less, has demonstrated significant potential in enhancing metabolic health and modulating body composition through the optimization of circadian rhythms. This randomized controlled trial aimed to evaluate the effects of TRE compared to a Mediterranean Diet on body weight, overall body fat percentage, and visceral adipose tissue (VAT) mass via dual x-ray absorptiometry (DXA) scans in a population of adults with MetS. A total of 122 individuals were randomized 1:1 to a TRE arm and a standard of care (SOC) arm for 10 weeks. This study found significant differences between the SOC and TRE groups, with the TRE group exhibiting a greater mean weight reduction (-6.57 lbs) compared to the SOC group (-2.89 lbs) from baseline to the end of the 10-week intervention period ($p = 0.015$). Regarding overall fat percentage, the TRE group demonstrated a significantly larger mean change (-1.36%) compared to the SOC group (-0.115%), indicating a more substantial reduction in body fat($p = 0.005$). Evaluation of VAT mass revealed that the TRE group experienced a significantly greater reduction compared to the SOC group, even after adjusting for baseline VAT mass ($p < 0.001$). Notably, males in the TRE group exhibited a pronounced effect, with an additional average decrease of -66.44 g in VAT mass compared to females. These findings suggest that TRE has favorable effects on weight loss, overall fat percentage, and VAT mass reduction. The results highlight the potential of TRE as an effective dietary intervention for improving body composition and reducing visceral adiposity. Further research is warranted to elucidate the underlying mechanisms and evaluate the long-term sustainability of these effects.

INTRODUCTION

High systolic blood pressure, elevated fasting plasma glucose levels, increased body mass index (BMI), and elevated low-density lipoprotein (LDL) cholesterol levels are identified as prominent risk factors for global mortality.[1]. Such cardiometabolic conditions, coupled together, comprise the pathologic condition known as Metabolic syndrome (MetS). Individuals living with Metabolic Syndrome (MetS) exhibit a state of chronic inflammation within the body, distinguished by the presence of insulin resistance, hyperlipidemia, hypertension, and excessive adiposity in the abdominal region. [2,3,4] Metabolic Syndrome affects a significant portion of the population in the United States, with over 34% of adults estimated to be living with this condition according to the CDC.[3] The prevalence of Metabolic Syndrome increases with age, with nearly 50% of adults over the age of 60 having the condition. These figures are troubling as living with Metabolic Syndrome significantly increases risk of heart disease, stroke, and type 2 diabetes. [5]

Circadian Rhythms and Metabolism

A key regulatory component of metabolism, often overlooked, is the body's circadian rhythm. The circadian rhythm is a natural biological pattern that repeats approximately every 24 hours and affects the timing and function of biological and physiological processes in the body. This internal clock allows the body to adjust to the ongoing cycles of day and night. This rhythmicity allows for synchronization to environmental cues and behavioral patterns, enabling the circadian rhythm to be modified. [6] Thus, by strategically modulating the circadian rhythm, it is possible to enhance the optimization of the body's metabolic functioning and intricate biological processes. [7] As circadian rhythms control many aspects of our physiology, it affects sleep, hunger, and hormone production. Chronic circadian rhythm disruption, including round-

the-clock eating, can induce metabolic disorders by interfering with the intricate mechanisms governing energy homeostasis within the body. Chronic circadian rhythm has well-documented effects on glycemic control which can increase the risk of type 2 diabetes. [8]

Adiposity and Metabolic Syndrome

Visceral adipose tissue is fat that is accumulated in the abdominal cavity around internal organs. This form of fat is metabolically active, producing inflammatory chemicals and hormones that can interfere with regular metabolic processes.[9] This relationship between VAT mass and higher health risks underscores the importance of reducing VAT mass in those living with MetS. Furthermore, excess VAT is associated with insulin resistance, persistent low-grade inflammation, and dyslipidemia, all of which are significant markers of MetS.[10,11] Thus, lowering VAT may serve as a powerful means for individuals with MetS to improve their metabolic profile, including insulin sensitivity, cholesterol levels, and inflammatory markers, by lowering VAT. This reduction can lead to better blood sugar management, improved lipid profiles, and a lower risk of cardiovascular disease and type 2 diabetes.

Although pharmacological treatment can play a significant role in the management of MetS, lifestyle interventions such as moderating nutrition intake and increasing physical exercise are also recommended in addition to drug therapy.[12] Extensive scientific evidence supports the notion that weight loss has consistently yielded favorable outcomes in the management of metabolic syndrome. Recent research has consistently shown that intentional weight loss achieved through lifestyle interventions, which include dietary changes and increased physical activity, has a positive effect on multiple components of metabolic syndrome, including insulin resistance, dyslipidemia, and blood pressure.[13,14] Despite the widespread efforts among nearly half of US adults to pursue weight loss annually, the prevalence of obesity and severe obesity

remains persistently on the rise.[15] Existing scientific literature has consistently demonstrated that individuals facing socioeconomic disadvantages bear a higher susceptibility to the development of Metabolic Syndrome (MetS). Consequently, directing research efforts towards the formulation of pragmatic and economically viable lifestyle interventions becomes imperative. By prioritizing the investigation of feasible and affordable approaches, we can bridge the gap and ensure equitable access to effective interventions for mitigating the risk and burden of MetS within disadvantaged populations.[16,17]

Time-Restricted Eating

An emerging avenue for the promotion and maintenance of robust circadian rhythms is time-restricted eating (TRE), which involves limiting the time period during which food is consumed each day, typically to 10 hours or less. This practice has garnered scientific interest due to its potential impact on body weight regulation and metabolic health. Preclinical research and clinical trials employing TRE have established the intervention's potential to ameliorate metabolic disorders in recent years.[18,19] It is plausible that orchestrating synchronization of the body's circadian rhythms through the promotion of a more regular eating schedule could potentially improve metabolic health. By doing so, it may allow for an extended duration of restorative metabolic activities within vital physiological systems. Prior research has demonstrated that TRE not only reduces appetite but also enhances fat oxidation, thus promoting fat loss.[20] This effect can be attributed to the prolonged fasting periods during TRE, which promote the utilization of stored fat as an energy source. TRE has also been shown to improve insulin sensitivity and regulates metabolic hormones such as leptin and ghrelin, which contribute to appetite control and fat metabolism.[21] These recent findings suggest that implementing TRE

may have potential as a multidimensional weight management and metabolic health improvement therapy.

The purpose of our study is to measure the health impact of TRE in patients with Metabolic Syndrome, and particularly its effect on weight, overall body fat percent, and visceral adipose tissue (VAT) mass in a randomized-controlled trial. In this randomized-controlled trial, participants were randomly assigned to either a control group receiving behavioral nutrition counseling or an intervention group receiving behavioral nutrition counseling with the addition of adopting a 10-hour eating window for 12 weeks. By examining the effects of TRE in patients with MetS, we hope to contribute to a better understanding of how circadian rhythms and time-restricted eating can be used to improve metabolic health. Through a comprehensive investigation of the effects of TRE in individuals diagnosed with Metabolic Syndrome (MetS), our endeavor aims to augment the existing body of knowledge pertaining to the intricate interplay between circadian rhythms, metabolic health, and the potential therapeutic benefits of TRE. The study's findings may help elucidate the mechanisms underlying the relationship between circadian rhythm disruption and metabolic syndrome, highlighting the potential role of regular eating patterns in improving metabolic health outcomes and ensuring their relevance and applicability in real-world settings.

METHODS

Trial Design

This study was a randomized clinical trial conducted at the University of California, San Diego (UCSD). This study was granted approval by the UCSD Institutional Board of Review and all participants underwent a formal informed consent process. Before the study began, the study statistician created a study randomization table using the SPSS program with block sizes of 4 and 6. Participants were randomized (1:1 ratio) to either the control group or the intervention group. The control arm, or standard of care (SOC) group, received general nutrition counseling and was recommended a Mediterranean Diet.[22] The intervention group (TRE) received that same standard of care as the SOC group, in addition to self-selecting a designated eating window for all dietary intake where the interval outside of the window was dedicated to fasting.

Participants

Study participants were between the ages of 18 and 65 and met criteria for metabolic syndrome (MetS). Inclusion criteria for MetS was characterized by clinical features including a BMI ≥ 25 and the presence of at least three of the following criteria: Elevated fasting plasma glucose ≥ 100 mg/dL, fasting plasma triglycerides ≥ 100 mg/dL, systolic blood pressure $\geq$ 135mmHg, diastolic blood pressure ≥ 85 mmHg as measured via fasting blood draw during the screening process.[23] Patients undergoing pharmacotherapy for any of the aforementioned criteria were accepted as fulfilling the criteria as well. Inclusion criteria required that participants had a self-reported window of dietary intake that was greater than 12 hours per day. Study participants were required to record all consumption of food, beverage, and medications in the myCircaidanClock (mCC) mobile application.[24] Pregnant or breast-feeding women, patients with diabetes diagnosis, patients with history of substance use including tobacco, patients living with

HIV, patients that have undergone surgery for weight management, and patients with a history of any major adverse cardiovascular event were excluded from the study as the safety of TRE is not well-explored in these populations. Participants were recruited via Electronic Medical Record systems. This study was also registered and active for recruitment on Clinicaltrials.gov. Furthermore, promotional materials including flyers and business cards were distributed to primary care providers and obesity clinics around San Diego.

Study Procedures

Each participant underwent a 2-week screening period where baseline eating patterns and pre-intervention clinical values were recorded. After the 2-week screening period, if the participant met the ≥ 12-hours eating window and the mCC app logging requirements, they were randomized (1:1) to either the standard-of-care arm or the time-restricted eating arm for 10 weeks. The study statistician created a randomization table and used a block randomization schema with both block sizes of 4 and 8 to minimize selection bias.

As the standard-of-care protocol, all study participants, regardless of their study arm, received nutrition counseling upon randomization and were recommended a Mediterranean diet. The Mediterranean diet is a dietary pattern that emphasizes a high intake of fruits, vegetables, whole grains, legumes, nuts, and olive oil while limiting intake of red meat and processed foods. It also includes moderate amounts of fish, chicken, and dairy products. Numerous health advantages have been linked to the Mediterranean Diet, including a lower risk of diabetes, cardiovascular disease, and several types of cancer. Sustained adherence to the Mediterranean diet was associated with a lower risk of cardiovascular events, mortality, and incidence of stroke and heart disease.[25] The Mediterranean diet has demonstrated feasibility and acceptability in

MetS and overweight populations, and has demonstrated positive effects on cardiometabolic biomarkers.[26]

Those randomized to the TRE arm were required to select an 8 to 10-h window for all dietary consumption where the remaining 14-16 hours in the day are allocated to fasting. Typically, individuals who consumed calories for 14 or more hours daily were instructed to choose a 10-hour eating window, whereas those with a daily consumption period of 12-14 hours were advised to select an 8-hour window. The selected window of consumption was determined based on the participants' window of food and beverage consumption prior to starting the study. This individualized approach established a specific and constant eating window throughout the 10 weeks in the intervention phase, such as 8 a.m. to 6 p.m. Individuals could consume their meals and caloric intake during their designated window, but only calorie-free liquids such as water or unsweetened tea were permitted outside of this time frame. Maintaining consistent timing of food intake was a particularly important aspect of the study, as the primary aim of TRE was to align fasting and feeding patterns with the body's circadian rhythms.

Clinic Visit 1

During the first visit (Visit 1), which marked the start of the 2-week baseline, study coordinators facilitated a formal informed consent process with each study participant. Following the consent process, participants underwent a fasting blood draw to assess a range of cardiometabolic biomarkers, accompanied by the measurement of their heart rate, blood pressure, and weight by a nurse in the clinic. The following validated methods were used to measure baseline values: blood pressure measurements using an Welch AllynBP blood pressure cuff[27], fasting blood draw to measure LDL cholesterol via Nuclear Magnetic Resonance LipoProfile®[28] , fasting plasma glucose test, as well as a fasting triglyceride test, weight

measurement using a Tanita scale [29], and mid-waist measurement according to National Institutes of Health[30] guidelines. These measurements served the dual function of qualifying participants for the study based on inclusion criteria and establishing their baseline levels. At the end of this visit, participants were introduced to the mCC app and instructed on its use in order to document all oral intake. Following Visit 1, participants entered a 2-week baseline period during which they were required to use the mCC app to document their regular baseline eating patterns prior to the intervention start.

Clinic Visit 2

During the second visit (Visit 2), which concluded the 2-week baseline window, participants who met the ≥12 hours daily eating window criteria, were asked to return to the ACTRI clinic. Participants who met all screening criteria were then randomly assigned (1:1) to either the standard of care (SOC) or the time-restricted eating (TRE) group. At this time, a baseline Dual-energy X-ray absorptiometry (DXA) scan was performed on all participants, regardless of group assignment. DXA scan was used as it has extensively studied as a reliable method for assessing body composition and has been validated against gold standard methods for body composition assessment.[31] Each participant was also counseled by a study dietitian who reviewed the principles of Mediterranean diet[22] and information on their assigned eating pattern for the next 10 weeks.

For those in the TRE intervention group, the study coordinators aided each participant in selecting a 8-hour or 10-hour eating interval that suits their lifestyle based on their baseline eating pattern. The chosen interval was then entered into the app, which allowed participants to visualize their daily eating pattern to ensure they consumed all meals within that time. While all participants were educated about the Mediterranean diet and encouraged to implement it in their

daily lives, TRE was the only intervention in this study. The control group received standard health and wellness guidelines, with particular regard for the Mediterranean diet, and was advised to continue their usual eating pattern that is greater than 12 hours. Both groups were instructed to continue using the mCC app to document all dietary intake, exercise, and sleep quantity/quality for at least 1 week every month.

Clinic Visit 3

The third visit primarily served as a check-in point at the 8-week mark of the 10-week intervention period. The study team reviews activity on the mCC app and reminds each participant to document all oral intake, exercise, and sleep quantity/quality.

Clinic Visit 4

At the final visit, scheduled at the end of the 10-week intervention period, participants were required to come into the clinic for a final visit. During this visit, various measurements and assessments were conducted. Height, weight, BMI, waist circumference, and resting blood pressure will be measured. Additionally, participants will complete the same general health questionnaires as in Visit 1. A full-body DXA scan will also be conducted to assess body composition. Finally, participants will have a final check-in with a study dietitian.

Study Outcomes

Body fat percentage, weight, and visceral adipose tissue were the main outcomes of interest. The intervention group, which distinguished between people allocated to the TRE intervention and those in the SOC group, was the primary predictor variable. To account for potential confounding variables, age, sex, race, and baseline adiposity were also thought to be significant covariates and included as additional predictors in the study.

Statistical Analysis

Data from the study was analyzed using an intent-to-treat protocol. All of the 108 participants who completed the study were included in the preliminary analysis and a sub-analysis was performed for participants that began the study with outlying baseline data. Using independent sample t-tests, the major outcomes—body fat percentage, weight, and visceral adipose tissue—will be contrasted between the intervention group (TRE) and the standard-of-care (SOC) group. Pairwise t-tests were used to look at differences between groups from pre- to post-intervention. Additionally, age, sex, and race will be added as covariates in the multivariable models to account for any confounding factors. Regression models will be used in the multivariable analysis to analyze the relationship between the intervention group and the primary outcomes while controlling for covariates. A sample size of 108 participants gives the study analysis a power of 80% at minimum, at significance level of alpha=0.05, which is sufficient to detect a medium effect size using G*Power.[32] Data was analyzed using the R statistical software, RStudio (V1.1.4).[33]

RESULTS

Participants and Retention

286 volunteers were screened for eligibility in this randomized controlled trial between April 29, 2019, and October 24, 2022. 122 individuals were randomly divided into two groups: 61 to TRE and 61 to SOC. The 3-month intervention period was successfully completed by 108 out of 122 individuals with a retention rate of 89%. A total of 14 participants (7 SOC and 7 TRE) did not complete the intervention; however, none of these participants withdrew from the study due to severe adverse effects associated with the intervention (Figure 1). While the control group (SOC) had an average age of 61.43 years (1.25), the trial group (TRE) had a slightly lower average age of 56.78 years (1.54). Although these values are clinically similar, there was a statistically significant difference in age (Welch t-test, $p= 0.02$). As age was the only measured value that was statistically different between the two groups at baseline, it was later adjusted for via multivariable modeling. The TRE group had 26 males (48.1%) and 28 females (51.9%) and the SOC group had 27 males (50%) and 27 females (50%) (Table 1). Moreover, participants in both groups had similar baseline characteristics, with 72% of all participants taking one or more drugs to support their cardiometabolic health (Table 1).

Body Weight

The analysis revealed a statistically significant difference in weight change between the SOC (-2.89 lbs) and TRE (-6.57) lbs intervention groups (Welch t-test, $p= 0.015$) from baseline to post-intervention (Table 2). A linear regression model assessed the effect of race (White vs. non-White) on weight change between intervention groups from baseline to post-intervention, which was not found to be significant in this model ($\beta=0.983$, $p= 0.722$). A separate linear regression model assessed the effect of sex on weight change between intervention groups from

baseline to post-intervention, which was also not found to be significant in this model (β=-1.463, p= 0.606). As previously indicated, age was appropriately accounted for through multivariable modeling since it was identified as differing between the SOC and TRE group. Nevertheless, the analysis conducted using multivariable linear modeling did not reveal a significant impact of age on weight change between the SOC and TRE group (β=-0.06, p= 0.411). These results indicate that race, age, and sex had no significant effect on the observed weight fluctuations in this study population.

Overall Fat Percent

A significant difference was observed for the change in total body fat percentage (%) between the SOC and TRE intervention groups (Welch t-test, p-value = 0.005). The mean change in body fat percentage for the SOC group was -0.115%, indicating a slight reduction, while the TRE group exhibited a significantly greater mean change of -1.36%, indicating a more substantial decrease in body fat (Figure 3 and Table 2). A linear regression model was performed to examine the relationship between total body fat percentage, intervention group, and sex to see if sex demonstrated an interaction. However, the analysis did not find that sex had a significant interaction on total body fat percent change between groups (β=-0.757, p= 0.084). The association between total body fat percentage, intervention group, and race (White (n=68) vs non-White (n=38)) was also investigated using a linear regression model. The variable of race revealed that when compared to non-White participants (mean=-0.234%), White participants (mean=-1.06%) had a greater decrease in total body fat on average (p=0.042) from baseline to post-intervention. Age was also accounted for when looking at overall fat percent using multivariable linear modeling since it was identified as differing between the SOC and TRE

group. The multivariable analysis did not reveal a significant impact of age on overall body fat percentage between groups (β=-0.717, p= 0.197).

Visceral Adipose Tissue (VAT) Mass

A comparison of changes in visceral adipose tissue (VAT) mass revealed that the SOC group had a mean reduction in VAT mass of -20.019 g, while the TRE group had a higher mean reduction of -64.56 g (Table 2). When adjusting for baseline VAT mass, the TRE group saw a significantly greater loss in VAT mass than the TRE group from baseline to post-intervention (Welch t-test, $p<0.001$) (Figure 4). A linear regression model was used to investigate whether gender had an interactive effect on change in VAT mass between the two study arms. On average, a greater reduction in VAT mass was observed among males in the TRE group, with an observed additional decrease of -66.44g on average in VAT mass in comparison to females from baseline to post-intervention (β=-66.44, p= 0.012). Given the difference in VAT mass, the VAT mass distributions for both sexes were tested for normality and were both found to have normal distributions. No significant differences were observed between groups from baseline to post-intervention in VAT mass when examining race (White vs. Non-white) in (β=-45.82, p= 0.096). Multivariable linear modeling was used to assess the effect of age on VAT mass, taking into account the identified age differences between the standard of care (SOC) and time-restricted eating (TRE) groups. The multivariable analysis revealed that age had no statistically significant effect on overall body fat percentage between groups (β =-0.818, p = 0.530).

DISCUSSION

The present RCT demonstrates significant improvements in several important indicators of body composition and subsequent cardiometabolic health through the implementation of TRE. The study findings reveal that TRE has favorable effects on weight, overall body fat percentage, and VAT mass. These effects were observed alongside the standard of care provided by the Mediterranean diet in addition to medications. The study effectively recruited a significant number of participants and had a high retention rate across the 3-month intervention period, supporting study feasibility and adherence. The absence of serious side effects linked with the intervention adds to the study protocol's safety. The comparable baseline features across the TRE and SOC groups increase the validity of the randomization process and suggest that any observed benefits on cardiometabolic health outcomes can be attributed more confidently to the intervention itself rather than baseline variations.

Changes in Body Weight and Overall Fat Percentage

This clinical trial provides novel findings demonstrating that TRE improves weight (TRE=-6.57lbs; SOC=-2.89 lbs) and overall fat percentage (TRE=-1.36%; SOC=-0.115%) when compared to a control group following a standard, healthy dietary plan. The National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend a weight reduction of 10% for individuals that are looking to significantly reduce the risk of cardiovascular disease and associated biomarkers. However, much of the literature suggests that even a 3% to 5% reduction in weight can lead to a significant decrease in such health risks.[34,35] The significant weight loss and fat percentage loss in the TRE group also calls into question the consistency of some of the existing scientific literature on the subject. Two similar studies that recently examined the effects of TRE on weight found no significant differences between-groups for baseline and intervention.

However, both of these interventions required participants to consume calories in a preset interval of time, without the flexibility of having their eating window be set in accordance with their own daily sleep-wake cycles. [36,37] Although the present study required that the daily eating window stay the same throughout the study for each participant, the study design offered more flexibility for participants to initially set their eating window to the hours in the day that coincide best with their schedules. This customizable aspect inherent in the study design likely fostered greater adherence to the experimental protocol, while concurrently aligning more closely with participants' circadian rhythms, specifically with respect to their sleep-wake and activity cycles.

This study's findings that biological sex has no effect on weight or body fat percentage are generally consistent with the body of literature that has been published, especially when comparing the effects of diet and nutrition interventions and exercise-based interventions on differences in weight and fat percentage outcomes.[38] Race also did not demonstrate a significant effect on overall weight loss between groups from baseline to post-intervention. Furthermore, race did not demonstrate a significant effect on VAT mass between groups from baseline to post-intervention. However, White study participants saw a marginally significantly greater change in overall fat percentage from baseline to post-intervention, compared to non-White study participants ($p=0.042$). Although the underpinnings of these findings are unclear, with only marginal significant differences, future research may benefit from increased inclusion of participants from underrepresented demographics in order to further explore such observed differences.

Changes in Visceral Adipose Tissue (VAT) Mass

Study data revealed that participants in the TRE group had a much higher reduction in VAT mass than participants in the SOC group. Importantly, even after controlling for baseline

VAT mass, the TRE group outperformed the SOC group in terms of VAT mass decrease ($p<0.001$). Prior literature has emphasized the notable role that loss of visceral adipose tissue has on overall weight and metabolic health. VAT has high metabolic activity and has been linked to an increase in health risks such as cardiovascular disease and type 2 diabetes. Because visceral adipose tissue (VAT) has a higher metabolic activity than subcutaneous fat, reducing it is an important aspect in generating significant weight loss and improving overall body composition, which is consistent with the findings of this study.[39,40,41] Thus demonstrating that TRE may be a useful tool in not only improving weight and body composition, but metabolic activity as well.

Furthermore, study results revealed an intriguing interaction, as males in the TRE group experienced a pronounced effect with an additional average decrease of -66.44 g in VAT mass compared to females. These findings suggest that TRE may have a more pronounced impact on VAT reduction among male participants. Similar health behavior intervention trials have been performed exploring body composition outcomes, revealing similar findings that, on average, males are more likely than women to lose visceral adipose tissue (VAT) mass.[42,43] The robust scientific evidence supporting this claim suggests the inevitable role of genetic sex differences and hormone profiles that underpin visceral adiposity.[44] Further research, including profiling of sex hormones, may be warranted to elucidate the underlying mechanisms.

Strengths and Limitations

The study design encompassed several strengths including the combination of TRE with standard-of-care and in comparison to standard of care treatments. The use of a larger sample size and the adoption of a randomized controlled trial (RCT) design in this study facilitated comparison of the outcome variable and robust establishment of causality. This approach proved effective in minimizing the influence of confounding variables, which is of particular importance

given the study population's considerable burden of comorbidities. The intervention also allowed personalization for study participants including being able to set specific eating windows. Furthermore, using the mCC app to document nutrient intake rather than a traditional manual written log provided a technologically enhanced approach and a layer of convenience to the study design. Furthermore, implementing the intervention in the real-world setting of participants' homes provided a contextually meaningful and realistic environment for implementation of the intervention.

One of the primary limitations was the study's relatively short duration of three months, which may necessitate longer trials lasting a year or more in the future in order to fully explore the long-term effects of TRE. Additionally, although 108 participants provided for a medium effect size, future studies may benefit from having more participants for a larger effect size. Additionally, adherence to protocol and report of dietary consumption patterns depended on self-reported which faces inherent bias and bears the risk of underreporting. Moreover, the study lacked the statistical power to conduct an in-depth investigation of ethnicity-based outcomes. However, the overall study enrollment demonstrated comparable representation of White participants and persons from minority backgrounds.

CONCLUSION

This randomized controlled experiment provides evidence that TRE has a positive effect on weight, overall body fat percentage, and visceral adipose tissue (VAT) mass. The trial exhibited significant retention and adherence rates, underlining the intervention's feasibility and safety. The observed benefits of TRE with regard to weight and overall body fat percentage were irrespective of gender and race, implying that the findings are applicable to a wide range of populations. The adjustable component of TRE, which allowed individuals to coordinate their eating window with their sleep-wake cycles, most likely contributed to higher adherence and maybe improved outcomes. These findings highlight the potential applicability of TRE in clinical practice and emphasize the significance of additional research to validate and expand on these findings, particularly with longer-term trials and the inclusion of underrepresented populations. The study's strengths, such as the use of TRE in conjunction with standard-of-care as well as the setting of a real-world situation, increase its validity and relevance.

Additional research is required to confirm and build on these findings and longer trials lasting a year or more would provide a more complete picture of the long-term advantages and potential pitfalls of this dietary regimen. Although continuous glucose monitoring was used for a total of 4 weeks of the study, future research may consider using such objective metrics to assess adherence to food consumption for the full duration of the study. While the study showed the potential benefits of TRE and its application to a wide range of groups, more research is required to clarify the underlying mechanisms causing the observed results. Understanding the physiological and metabolic pathways by which TRE affects body composition and cardiometabolic health would help to design focused interventions and individualized recommendations.

The study findings demonstrate that tailoring TRE to individuals' sleep-wake cycles has great potential to improve fat composition. The findings highlight the potential of TRE in targeting VAT reduction, particularly for men, and advocates for additional research to examine processes and validate connections.While the current study provides important insights into the beneficial effects of TRE on body composition and cardiometabolic health, more research is needed to validate and expand on these findings. Longer-term trials, objective adherence measures, increasing participation of underrepresented populations, and mechanistic research would improve our understanding of the potential benefits and maximize the use of time-restricted eating in clinical practice.

References

1. Murray CJL, Aravkin AY, Zheng P, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020;396(10258):1223-1249.

2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet.* 2005;365(9468):1415-1428.

3. Moore JX, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. *Prev Chronic Dis.* 2017;14:E24.

4. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12.

5. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165(22):2644-2650.

6. Becker GJ. The National Institute of General Medical Sciences. *J Am Coll Radiol.* 2005;2(9):790-792.

7. Chaix A, Manoogian ENC, Melkani GC, Panda S. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. *Annu Rev Nutr*. 2019;39:291-315.

8. Mason IC, Qian J, Adler GK, Scheer FAJL. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. *Diabetologia*. 2020;63(3):462-472.

9. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *Br J Radiol.* 2012;85(1009):1-10.

10. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes*. 2012;19(2):81-87.

11. Bosello O, Zamboni M. Visceral obesity and metabolic syndrome. *Obes Rev*. 2000;1(1):47-56.

12. Sperling LS, Mechanick JI, Neeland IJ, et al. The CardioMetabolic Health Alliance: Working Toward a New Care Model for the Metabolic Syndrome. *J Am Coll Cardiol*. 2015;66(9):1050-1067.

13. Stelmach-Mardas M, Rodacki T, Dobrowolska-Iwanek J, et al. Link between Food Energy Density and Body Weight Changes in Obese Adults. *Nutrients*. 2016;8(4):229.

14. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical

practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol.* 2020;16(3):177-189.

15. CDC. Adult obesity facts. Centers for Disease Control and Prevention. Published July 20, 2022. Accessed June 10, 2023. https://www.cdc.gov/obesity/data/adult.html

16. Hostinar CE, Ross KM, Chen E, Miller GE. Early-Life Socioeconomic Disadvantage and Metabolic Health Disparities. *Psychosom Med*. 2017;79(5):514-523.

17. Loucks EB, Magnusson KT, Cook S, Rehkopf DH, Ford ES, Berkman LF. Socioeconomic position and the metabolic syndrome in early, middle, and late life: evidence from NHANES 1999-2002. *Ann Epidemiol*. 2007;17(10):782-790.

18. Wilkinson MJ, Manoogian ENC, Zadourian A, et al. Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. *Cell Metab*. 2020;31(1):92-104.e5.

19. Chaix A, Lin T, Le HD, Chang MW, Panda S. Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. *Cell Metab*. 2019;29(2):303-319.e4.

20. Ravussin E, Beyl RA, Poggiogalle E, Hsia DS, Peterson CM. Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans. *Obesity* . 2019;27(8):1244-1254.

21. Antoni R, Johnston KL, Collins AL, Robertson MD. Effects of intermittent fasting on glucose and lipid metabolism. *Proc Nutr Soc*. 2017;76(3):361-368.

22. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the Mediterranean Diet; a Literature Review. *Nutrients*. 2015;7(11):9139-9153.

23. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645.

24. Manoogian ENC, Wei-Shatzel J, Panda S. Assessing temporal eating pattern in free living humans through the myCircadianClock app. *Int J Obes* . 2022;46(4):696-706.

25. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr*. 2018;72(1):30-43.

26. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Ann Intern Med*. 2009;151(5):306-314.

27. Alpert BS. Clinical evaluation of the Welch Allyn SureBP algorithm for automated blood pressure measurement. *Blood Press Monit*. 2007;12(4):215-218.

28. Smy L, De Biase I, Genzen JR, Yuzyuk T. The nuclear magnetic resonance metabolic profile: Impact of fasting status. *Clin Biochem*. 2021;87:85-92.

29. Ritchie JD, Miller CK, Smiciklas-Wright H. Tanita foot-to-foot bioelectrical impedance analysis system validated in older adults. *J Am Diet Assoc*. 2005;105(10):1617-1619.

30. Ma WY, Yang CY, Shih SR, et al. Measurement of Waist Circumference: midabdominal or iliac crest? *Diabetes Care*. 2013;36(6):1660-1666.

31. Haarbo J, Gotfredsen A, Hassager C, Christiansen C. Validation of body composition by dual energy X-ray absorptiometry (DEXA). *Clin Physiol*. 1991;11(4):331-341.

32. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175-191.

33. RStudio Team. *RStudio: Integrated Development for R. RStudio*.; 2015. Accessed May 14, 2022. http://www.rstudio.com/

34. Key Recommendations. *Int J Tuberc Lung Dis*. 2022;26(1):8-11.

35. Donnelly JE, Blair SN, Jakicic JM, et al. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc*. 2009;41(2):459-471.

36. Liu D, Huang Y, Huang C, et al. Calorie Restriction with or without Time-Restricted Eating in Weight Loss. *N Engl J Med*. 2022;386(16):1495-1504.

37. Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity: The TREAT Randomized Clinical Trial. *JAMA Intern Med*. 2020;180(11):1491-1499.

38. Williams RL, Wood LG, Collins CE, Callister R. Effectiveness of weight loss interventions--is there a difference between men and women: a systematic review. *Obes Rev*. 2015;16(2):171-186.

39. Sowers JR. Obesity as a cardiovascular risk factor. *Am J Med*. 2003;115 Suppl 8A:37S - 41S.

40. Rana MN, Neeland IJ. Adipose Tissue Inflammation and Cardiovascular Disease: An Update. *Curr Diab Rep*. 2022;22(1):27-37.

41. Hanlon CL, Yuan L. Nonalcoholic Fatty Liver Disease: The Role of Visceral Adipose Tissue. *Clin Liver Dis*. 2022;19(3):106-110.

42. Redman LM, Heilbronn LK, Martin CK, et al. Effect of calorie restriction with or without exercise on body composition and fat distribution. *J Clin Endocrinol Metab*. 2007;92(3):865-872.

43. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr*. 2008;99(5):931-940.

44. Vissers D, Hens W, Taeymans J, Baeyens JP, Poortmans J, Van Gaal L. The effect of exercise on visceral adipose tissue in overweight adults: a systematic review and meta-analysis. *PLoS One*. 2013;8(2):e56415.

APPENDIX

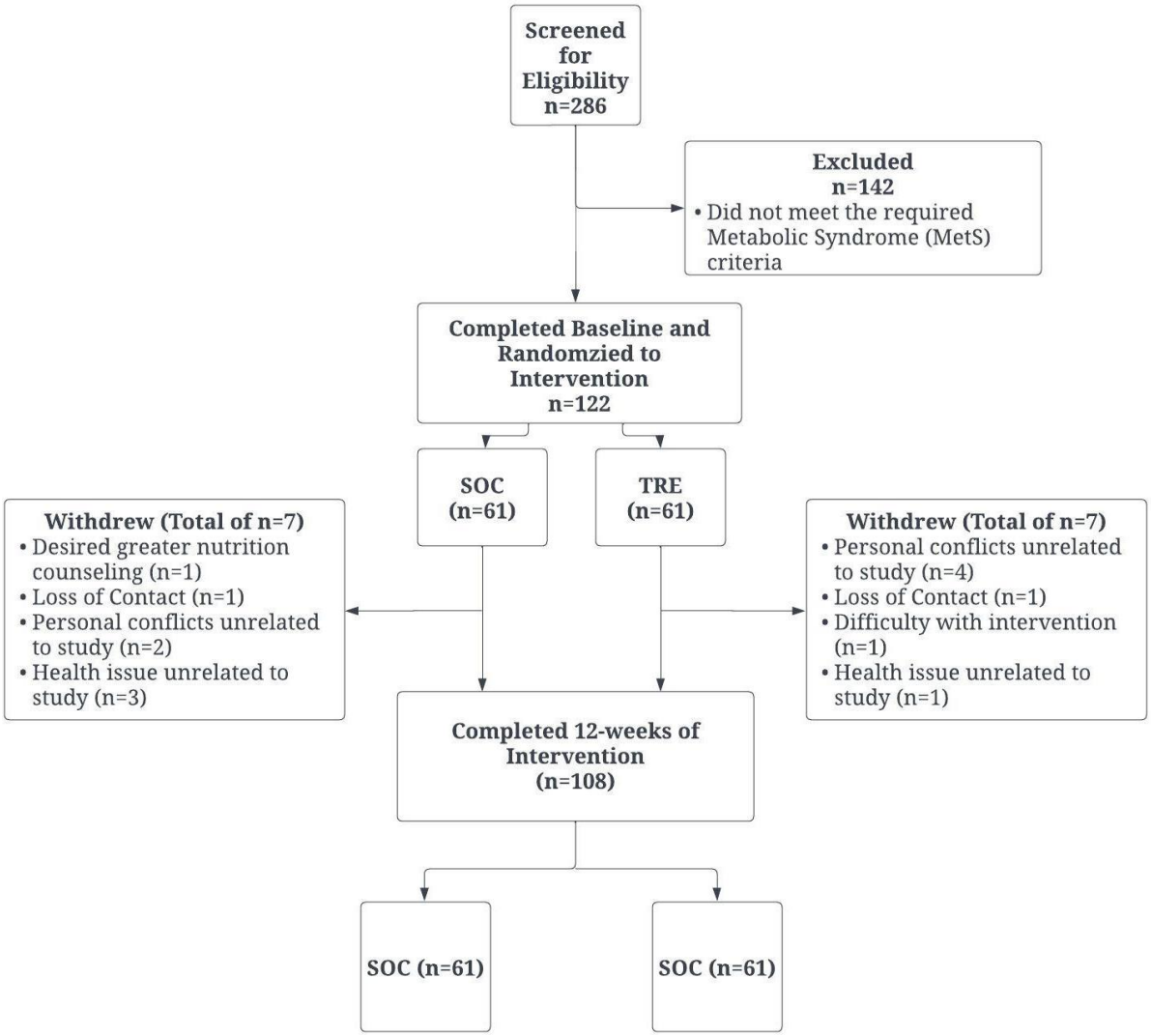

Figure 1. CONSORT Diagram

Table 1. Baseline Characteristics

Variable	**TRE (n=54)**	**SOC (n=54)**
Age (years)*	56.78 (1.54)	61.43 (1.25)
Sex N(%) - Males - Females	 26 (48.1%) 28 (51.9%)	 27 (50%) 27 (50%)
Race - White, n (Hispanic/Latinx n) - Asian, n (Hispanic/Latinx n) - Black, n (Hispanic/Latinx n) - Native Hawaiian or Other Pacific Islander, n (Hispanic/Latinx n) - Mixed Race, n (Hispanic/Latinx n) - Decline to State race/ethnicity, n (Hispanic/Latinx n)	 32 (1) 9 (0) 7 (0) 1 (0) 3(1) 2	 36 (1) 13 (0) 1 (0) 0 4(2) 0
Baseline Eating Window (hours)	14.38	14.00
Weight (lbs)	198.28 (37.44)	196.76 (36.34)
Overall Body Fat Mass (%)	37.7	38.26
Visceral Adipose Tissue (VAT) mass (g)	977.52 (271.18)	1050.24 (256.70)
BMI, kg/m^2	31.50 (0.55)	30.95 (0.55)

**Indicates significance at* $\alpha<0.05$

Table 2. Comparison of Study Outcomes in the SOC and TRE Groups

Outcome	SOC Group	TRE Group	P-value (Between Groups)
VAT Mass (g)	-64.56 (p<<0.001)***	-20.019 (p=0.349)	<0.001***
Weight Change (lbs)	-6.57 (p<<0.001)***	-2.89 (p<0.001)***	0.015**
Overall Fat Percent Change (%)	-1.36 (p<<0.001)***	-0.115 (p=0.703)	0.005**

Table 2 compares the outcomes of the SOC (Standard of Care) and TRE (Time-Restricted Eating) groups. VAT (Visceral Adipose Tissue) mass, weight change, and total fat % change are among the outcomes. The values show mean changes between and within each group from baseline (Week 0) to post-intervention (Week 12).
**Indicates significance at α<0.05*
***Indicates significance at α<0.01*
****Indicates significance at α<0.001*

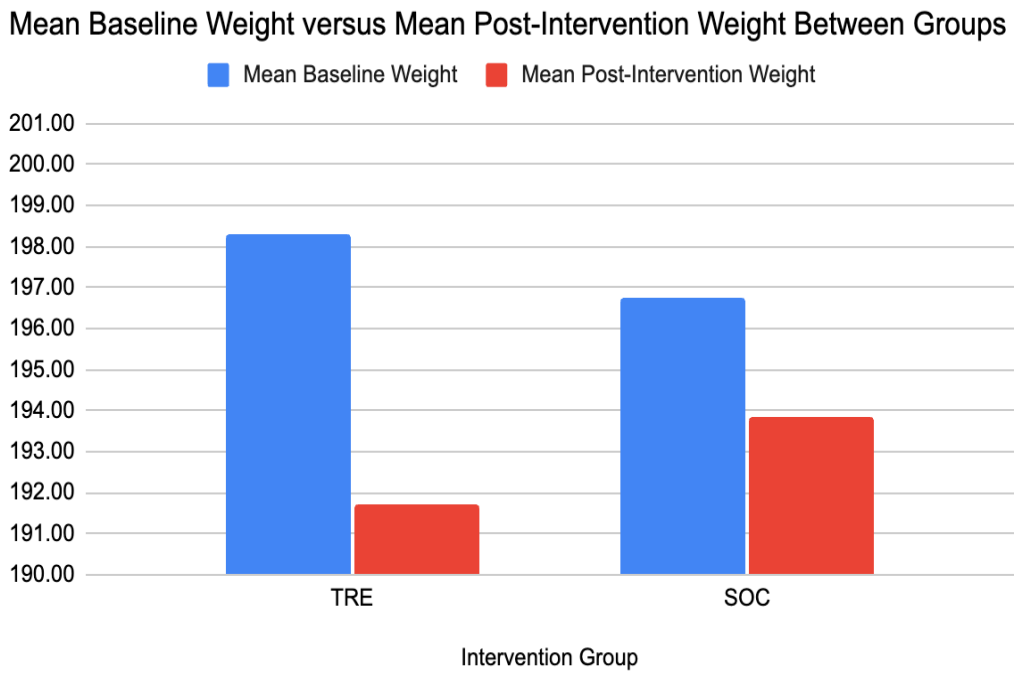

Figure 2. Differences in Mean Baseline Weight (lbs) versus Mean Post-Intervention Weight (lbs) Between Groups

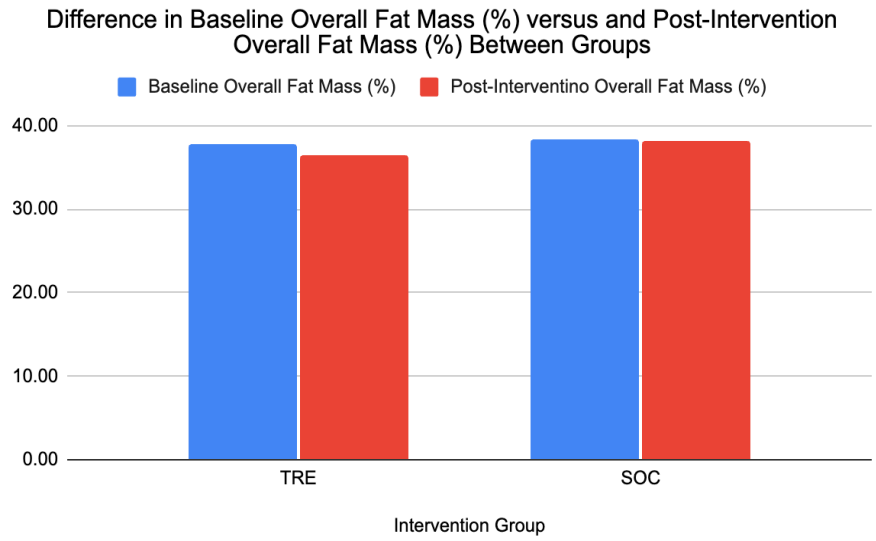

Figure 3. Differences in Mean Baseline Overall Fat Mass (%) versus Mean Post-Intervention Overall Fat Mass (%) Between Groups

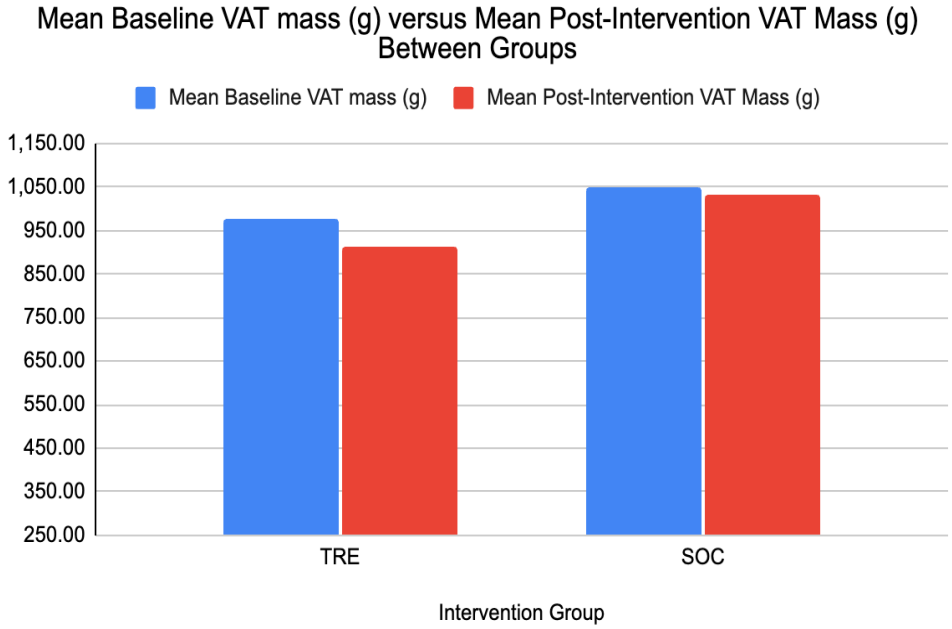

Figure 4. Differences in Mean Baseline VAT mass (g) versus Mean Post-Intervention VAT Mass (g) Between Groups