Time restricted eating with physical activity for weight management

Principal investigator:
Kelsey Gabel, Ph.D., RD
Clinical Assistant Professor and Postdoctoral Researcher
Department of Kinesiology and Nutrition
University of Illinois, Chicago
1919 West Taylor Street, Room 532
Chicago, Illinois, 60612
Tel: 312.413.8911
Email: kdipma2@uic.edu

Study location:
Human Nutrition Research Unit
1919 West Taylor Street, Room 121C
Chicago, Illinois, 60612

Coalition Strength and Conditioning
2051 W Carroll Ave
Chicago, IL 60612

Sponsor:
No sponsor.

Version 4

July 19, 2021

1.0 Eligibility

Older adults with overweight or obesity will be recruited by flyers posted around the University of Illinois at Chicago (UIC) campus and on social media. Subject eligibility will be assessed and determined by Kelsey Gabel Ph.D., R.D. Screening will be conducted in-person at the Human Nutrition Research Unit (HNRU) located in the Applied Health Sciences Building (1919 West Taylor St, Room 121C).

1.1 Inclusion criteria:

- Age between 50 to 70 years old
- BMI between 25 and 50 kg/m^2
- Pre-diabetic (fasting glucose: 100-125 mg/dl or HBA1c 5.7%-6.4%)
- Sedentary or lightly active [24]
- Are post menopausal (absence of menstural cycle for 1 year)

1.2 Exclusion criteria:

- Diabetic (fasting glucose: >126 mg/dl or HBA1c >6.5%)
- Have a history of eating disorders (anorexia, bulimia, or binge eating disorder)
- Have uncontrolled hypertension, any other cardiovascular disease, or history of aneurysm
- History of alcohol dependance (score >20 from Alcohol and Health Questionnaire)[25]
- Are not weight stable for 3 months prior to the beginning of study (weight gain or loss > 4 kg)
- Are not able to keep a food diary or activity log for 7 consecutive days during screening
- Are taking drugs that influence study outcomes (weight loss, glucose-lowering medications)
- Are premenopausal, perimenopausal or have an irregular menstrual cycle (menses that does not appear every 27-32 days)
- Mobility disability (unable to exercise for 40-60 minutes 3-5 days/week)
- Diagnosed comorbidities including systemic diseases (Parkinson's cirrhosis, renal disease or systemic rheumatic conditions), cancer, or cognitive impairment
- Are night shift workers
- Are smokers

2.0 Subject enrollment

Independently living subjects from the Chicago area will be recruited by flyers posted around the University of Illinois at Chicago (UIC) campus. The flyer will also be posted to social media outlets including: Instagram, Facebook, and Twitter. All study procedures will be conducted at the Human Nutrition Research Unit (HNRU) located in the Applied Health Sciences Building (1919 West Taylor St, Room 121C) .

Each subject will attend 1 screening visit. During **Visit 1** subjects will be screened by the Study Manager, Kelsey Gabel Ph.D., RD, via questionnaire, which will assess eligibility based on the requirements listed above. The following parameters will also be assessed: body weight and height (for BMI), a blood draw (for fasting glucose/diabetic status). Alcohol and Health Screening questionnaire will be administered to determine history of alcohol dependence (questionnaire is attached to submission). The Study Manager will also distribute a 7-day food record and provide detailed instructions on how to complete the records. Follow-up with participants virtually will be scheduled 10 days after the first screening. The food record will be assessed for adequacy (to evaluate each participant's motivation to participate in the study) and fasting blood glucose (via glucometer) will be taken. Consent will be obtained prior to the administration of the screening questionnaire by a member of the study team (key research personnel identified in Appendix P).

3.0 Study design and procedures

A 10-week non-randomized, controlled, parallel-arm trial, divided into a 2-week baseline and an 8-week intervention will be implemented. Older subjects with overweight or obesity (n = 20) will be assigned to 1

of 4 groups: (1) TRE (n = 5) ad libitum food intake from 12 pm to 8 pm, fasting (with zero-calorie beverages) from 8 pm to 12 pm daily, (2) TRE + EN (n = 5), TRE diet as stated in group 1 plus 3-4 days of 40-60 minutes of endurance exercise per week; or 3) TRE + RT (n = 5), TRE diet as stated in group 1 plus 3-4 days of 40-60 minutes of resistance training per week 4) control (n = 5), ad libitum food intake daily with no meal timing restrictions. In-person study activities will be carried out at the Human Nutrition Research Unit (HNRU) located in the Applied Health Sciences Building (1919 West Taylor St, Room 121C) or at Coalition Strength and Conditioning (2051 West Carroll Ave, Chicago IL 60612).

Diet and exercise interventions

Group	Diet protocol	Exercise protocol
TRE (n = 50)	8-h eating window Ad libitum food intake from 12-8 pm every day Fasting from 8-12 pm every day (16-h fast)	None
TRE + EN (n = 50)	8-h eating window Ad libitum food intake from 12-8 pm every day Fasting from 8-12 pm every day (16-h fast)	4 days/week, supervised 60 minutes, Intensity: 85% HRmax
TRE + RT (n = 50)	8-h eating window Ad libitum food intake from 12-8 pm every day Fasting from 8-12 pm every day (16-h fast)	4 days/week, supervised 60 minutes, Intensity: 85% RPE
Control (n = 50)	Every day: Ad libitum fed	No exercise

Diet protocol

TRE group and combination groups (8-h eating window): During the weight loss period, the TRE groups will be instructed to eat ad libitum from 12-8pm daily, and fast from 8-12 pm (16-h fast). During the 8-h eating window, there will be no restrictions on types or quantities of foods consumed. Moreover, participants will not be required to monitor caloric intake during this ad libitum feeding period. During the fasting period, participants will be encouraged to drink plenty of water and will be permitted to consume energy-free drinks, such as black tea, coffee, and diet sodas (limit 2 diet sodas/d, since these beverages may increase sugar craving [26]). TRE participants will meet with the dietitian every week (by phone or zoom) throughout the weight loss period to review their diet adherence. Subjects will also be taught how to make healthy food choices that conform to ADA nutrition guidelines.[27]

Exercise protocol

Study week	Week 1-2	Weeks 3-4
Exercise bouts/week	3	4
Endurance Training	Time: 40-50min Intensity: 65-75% HRmax	Time: 60 min Intensity: 85% HRmax
Resistance Training	Time: 40-50 min Intensity: 65-75% 1rm Protocol: 3x10-12reps	Time: 60 min Intensity: 75-85% 1rm Protocol: 3x8-12reps
	Increase intensity by 5-10% of 1RM when needed	

Endurance exercise combination group: Only the TRE + EN combination group will partake in the endurance exercise training. Participants will be given two supervised endurance exercise options due to COVID-19, one in-person and one remote. **Option 1 (in-person):** All training sessions will be conducted at the HNRU. Subjects will participate in a supervised aerobic exercise program 3-4 times per week, 40-60 min/d, for 8 weeks.[16,28] Exercise will be performed on an elliptical, stationary bike or rowing erg. Participants will be masked, exercise equipment will be placed ≥6ft apart and cleaned between use. During the week 1 sessions, subjects will exercise for 40 minutes at a moderate intensity (65% heart rate max (HRmax)). During the week 2 sessions, subjects will train for 50 minutes at a higher intensity (75% HRmax). For weeks 3-8, subjects will train for 60 minutes at an even higher intensity (85% HRmax). The participants will wear heart rate monitors (Fitbit Alta HR, Boston, MA) during each training session to provide visual feedback of their individualized target heart rate. Fitbit monitors will be distributed to subjects at each training session. **Compliance with the training:** A research assistant will be present to supervise all the training sessions. Exercise will be carefully documented through attendance at the training sessions. Subjects will be permitted to choose the day and time slot that works best for them. If a subject misses their session, they will be required to make up for it that same week. Subjects will be permitted to miss 4 sessions total during the 8-week intervention.

Option 2 (remote): All training sessions will be conducted at the subject's home. Subjects will participate in a supervised aerobic exercise program 3-4 times per week, 40-60 min/d, for 8 weeks.[16,28] Exercise will be performed by watching YouTube aerobic exercise (Zumba) videos at home. The video links will be provided by the study coordinator prior the exercise session. The coordinator conducting the study session on Zoom will have immediate knowledge of the subject's location so that they can relay this information to emergency personnel if needed. During the week 1 sessions, subjects will exercise for 40 minutes at a moderate intensity (65% heart rate max (HRmax)). During the week 2 sessions, subjects will train for 50 minutes at a higher intensity (75% HRmax). For weeks 3-8, subjects will train for 60 minutes at an even higher intensity (85% HRmax). The participants will wear heart rate monitors (Fitbit Alta HR, Boston, MA) during each training session to provide visual feedback of their individualized target heart rate. Fitbit monitors will be distributed to subjects so that they can monitor their heart rate at home. **Compliance with the training:** A research assistant will be present to supervise all the training sessions over Zoom. All sessions will be pre-scheduled with the research assistant, so the participant knows when to enter the Zoom meeting to perform the activity. Exercise will be carefully documented through regular online attendance at the training sessions. Subjects will be permitted to choose the day and time slot that works best for them. If a subject misses their session, they will be required to make up for it that same week. Subjects will be permitted to miss 5 sessions total during the 24-week trial.

Resistance training combination group (in-person): Only the TRE + RT combination group will partake in the resistance training exercise. All training sessions will be conducted in-person at the Coalition

Strength and Conditioning by Cole Cruz, MS, ACSM, CSCS. During the baseline period participants will attend two session prior to the intervention for familiarization and testing. The first session will be a familiarization session where the participant will be instructed on how to do the movements correctly and safely. The second session will test the participants' 5rm of deadlift, box squat, overhead press, and bench press. 1RM estimates will be based off of the 5rm (80% of 1rm)[29]. Subjects will participate in a supervised resistance training program beginning with 3 times per week progressing to 4 times per week in weeks 3-8 [16,30]. Each session will be 40-60 min in duration and will continue for 8-weeks[28,30,31]. During RT session participants will perform a progressive periodized whole-body resistance exercise (exercise program attached to submission). During the first 2 weeks of the RT program, the participants will complete three sets of 10–15 repetitions of 65% of their 1 rep max. For the following 6 weeks, the training volume will be set at three sets of 8–12 repetitions at an intensity of 75-85% of 1 rep max. Each week, weight will progressively increase by 5–10% as needed due to training adaptation. For all exercises, the participants will be instructed to perform each repetition in a slow, controlled manner, with a rest of 1-2 min between sets. The participants will wear heart rate monitors (Fitbit Alta HR, Boston, MA) during each training session to provide visual feedback of their individualized target heart rate. Fitbit monitors will be distributed to subjects at each training session. **Compliance with the training:** A research assistant will be present to supervise all the training sessions for compliance and correct technique execution. Exercise will be carefully documented through attendance at the training sessions. Subjects will be permitted to choose the day and time slot that works best for them. If a subject misses their session, they will be required to make up for it that same week. Subjects will be permitted to miss 4 sessions total during the 8-week intervention. (see COVID protocols in Subject Safety)

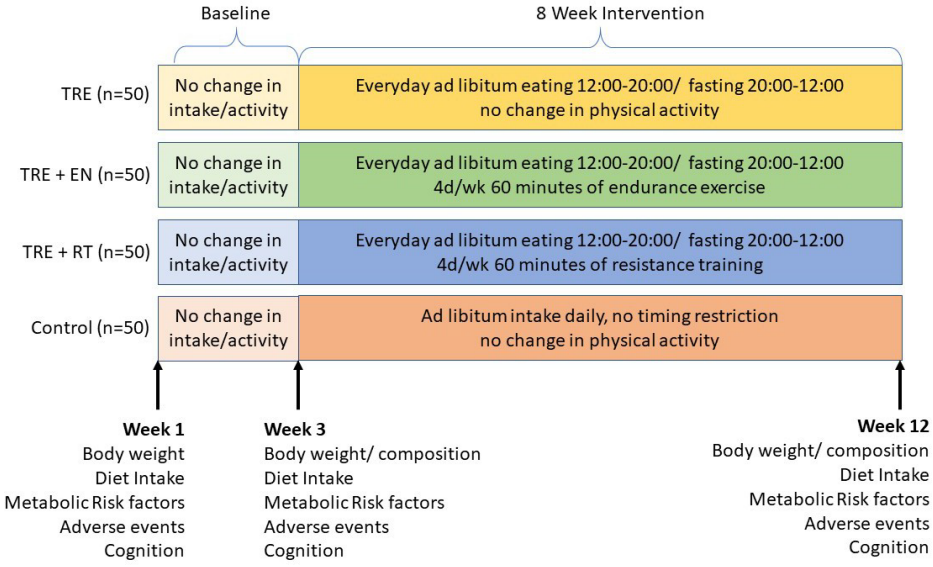
Control group protocol: Controls will be instructed to maintain their weight throughout the trial, and not to change eating or physical activity habits. Controls will visit the research center at the same frequency as the treatment groups (for outcome measurements) to control for investigator-interaction bias between groups. Controls will be offered free weight loss diet counseling (4 sessions) at the conclusion of the study by Kelsey Gabel, PhD., RD.

Weekly check-in: Weekly check-in calls will be done with all participants regardless of group at a prespecified time weekly via either zoom or telephone based on the participant preference. This appointment time will remain the same throughout the 10 weeks. During this call the study coordinator will address possible issues with compliance, difficulty with the intervention, and complete the adverse events questionnaire verbally. Time stamped weigh in photos and adherence logs will also be requested at this appointment. Further, dietary counseling to support the participant will be included in each call by a registered dietitian (Kelsey Gabel, PhD, RD). Diet counseling will not include weight loss counseling, but general lifestyle improvement so as can be also given to the control group for weight maintenance. All counseling will be based off of recommendations from the Academy of Nutrition and Dietetics, The American Heart Association, and Healthy People 2020. Topics will include:

- Increasing fruit and vegetable intake
- Reading food labels
- Water intake
- Lean protein
- Healthy fats
- Whole grains
- A balanced plate
  Choices for eating out

Subject compensation. No compensation or parking reimbursement is offered for trial completion. Participants will be able to have access to all data received from the study. In addition, controls will receive 4 free diet counseling sessions at the conclusion of the study.

Summary of intervention groups and key outcome measures



Study activities

Study activities		Baseline		Intervention (8 weeks)							
	Screen	1	2	3	4	5	6	7	8	9	10
Informed consent	•										
Screening/ Alcohol questionnaire	•										

Body weight	•	•	•	•	•	•	•	•	•	•	•
Waist circumference		•		•							•
Diet adherence		•		•	•	•	•	•	•	•	•
Fat mass (BIA)		•		•	•	•	•	•	•	•	•
Blood pressure/heart rate		•		•	•	•	•	•	•	•	•
DXA		•									
Blood draw	•	•		•							•
Activity monitor (7-d)		•									•
Food record		•		•							•
Sleep questionnaires		•		•							•
Adverse events survey		•		•	•	•	•	•	•	•	•
NeuroTrax Cognition		•		•							•
Quality of life/mood		•		•							•

4.0 Data analysis

Data will be analyzed by SPSS software (SPSS v24).

5.0 Statistical considerations

All continuous variables will be examined for distributions and the presence of outliers. Variables that are not normally distributed will be transformed and if normality cannot be achieved, will be analyzed using non-parametric tests. Standardized descriptive statistics including measures of means, median, standard deviations, ranges, and standard errors for continuous variables within each group will be calculated to describe the groups at fixed time points. Differences between groups at baseline will be assessed by a one-way ANOVA. A linear mixed model will be used to assess time, diet, and time × diet effects for each outcome. This model will provide unbiased estimates of time and treatment effects under a missing- at-random assumption. Time will not be assumed to be linear in the model. This strategy will allow for estimation of time and diet effects (and their interaction) without imposing a linear time trend. Relations between continuous variables will be assessed by Pearson's or Spearman's correlation coefficients as appropriate. Data will be analyzed using SPSS software (SPSS, Chicago, IL).

6.0 References

1. Prevention CfDCa. National Diabetes Statistics Report. Centers for Disease Control and Prevention, US Department of Health and Human Services 2020;2020.
2. Jensen GL, Hsiao PY. Obesity in older adults: relationship to functional limitation. Curr Opin Clin Nutr Metab Care 2010;13(1):46-51. DOI: 10.1097/MCO.0b013e32833309cf.
3. Willmann C, Brockmann K, Wagner R, et al. Insulin sensitivity predicts cognitive decline in individuals with prediabetes. BMJ Open Diabetes Res Care 2020;8(2). DOI: 10.1136/bmjdrc-2020-001741.
4. Ekblad LL, Rinne JO, Puukka P, et al. Insulin Resistance Predicts Cognitive Decline: An 11-Year Follow-up of a Nationally Representative Adult Population Sample. Diabetes Care 2017;40(6):751-758. DOI: 10.2337/dc16-2001.
5. United Nations DoEaSA, Population Division. World Population Ageing 2019. Highlights 2019;(ST/ESA/SER.A/430).
6. de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. N Engl J Med 2019;381(26):2541-2551. DOI: 10.1056/NEJMra1905136.
7. Patterson RE, Sears DD. Metabolic Effects of Intermittent Fasting. Annu Rev Nutr 2017;37:371-393. DOI:

10.1146/annurev-nutr-071816-064634.
8. Harvard University Health Blog. Intermittent fasting - Surprising update. (https://www.health.harvard.edu/blog/intermittent-fasting-surprising-update-2018062914156).
9. New York Times. Fasting diets are gaining acceptance. (https://well.blogs.nytimes.com/2016/03/07/intermittent-fasting-diets-are-gaining-acceptance/).
10. Associated Press. In a 24/7 food culture, periodic fasting gains followers. (https://apnews.com/f4d1474ebeb5492f8ce12c34266dfe93).
11. Gabel K, Hoddy KK, Haggerty N, et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. Nutr Healthy Aging 2018;4(4):345-353. (In eng). DOI: 10.3233/NHA-170036.
12. Cienfuegos S, Gabel K, Kalam F, et al. Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. Cell Metab 2020 (In eng). DOI: 10.1016/j.cmet.2020.06.018.
13. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA 2005;293(1):43-53. DOI: 10.1001/jama.293.1.43.
14. Das SK, Gilhooly CH, Golden JK, et al. Long-term effects of 2 energy-restricted diets differing in glycemic load on dietary adherence, body composition, and metabolism in CALERIE: a 1-y randomized controlled trial. Am J Clin Nutr 2007;85(4):1023-30. DOI: 10.1093/ajcn/85.4.1023.
15. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of Alternate-Day Fasting on Weight Loss, Weight Maintenance, and Cardioprotection Among Metabolically Healthy Obese Adults: A Randomized Clinical Trial. JAMA Intern Med 2017;177(7):930-938. DOI: 10.1001/jamainternmed.2017.0936.
16. Services DoHaH. Healthy People 2030. (https://health.gov/healthypeople).
17. Lee CG, Boyko EJ, Strotmeyer ES, et al. Association between insulin resistance and lean mass loss and fat mass gain in older men without diabetes mellitus. J Am Geriatr Soc 2011;59(7):1217-24. DOI: 10.1111/j.1532-5415.2011.03472.x.
18. Brochu M, Mathieu ME, Karelis AD, et al. Contribution of the lean body mass to insulin resistance in postmenopausal women with visceral obesity: a Monet study. Obesity (Silver Spring) 2008;16(5):1085-93. DOI: 10.1038/oby.2008.23.
19. Fukushima Y, Kurose S, Shinno H, et al. Importance of Lean Muscle Maintenance to Improve Insulin Resistance by Body Weight Reduction in Female Patients with Obesity. Diabetes Metab J 2016;40(2):147-53. DOI: 10.4093/dmj.2016.40.2.147.
20. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab 2011;96(9):2898-903. DOI: 10.1210/jc.2011-0435.
21. Moro T, Tinsley G, Bianco A, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. J Transl Med 2016;14(1):290. (In eng). DOI: 10.1186/s12967-016-1044-0.
22. Tinsley GM, Forsse JS, Butler NK, et al. Time-restricted feeding in young men performing resistance training: A randomized controlled trial. Eur J Sport Sci 2017;17(2):200-207. (In eng). DOI: 10.1080/17461391.2016.1223173.

23. Tinsley GM, Moore ML, Graybeal AJ, et al. Time-restricted feeding plus resistance training in active females: a randomized trial. Am J Clin Nutr 2019;110(3):628-640. DOI: 10.1093/ajcn/nqz126.
24. Pate RR, O'Neill JR, Lobelo F. The evolving definition of "sedentary". Exerc Sport Sci Rev 2008;36(4):173-8. DOI: 10.1097/JES.0b013e3181877d1a.
25. Bohn MJ BT, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. J STUD ALCOHOL 1995;Jul; 56(4):423-32. DOI: 0.15288/jsa.1995.56.423.
26. Swithers SE. Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 2013;24(9):431-41. DOI: 10.1016/j.tem.2013.05.005.
27. Evert AB, Dennison M, Gardner CD, et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care 2019;42(5):731-754. DOI: 10.2337/dci19-0014.
28. Edition. ACoSMt. ACSM's Guidelines for Exercise Testing and Prescription. : Lippincott Williams and Wilkins., 2017.
29. Reynolds JM, Gordon TJ, Robergs RA. Prediction of one repetition maximum strength from multiple repetition maximum testing and anthropometry. J Strength Cond Res 2006;20(3):584-92. DOI: 10.1519/R-15304.1.
30. Beavers KM, Ambrosius WT, Rejeski WJ, et al. Effect of Exercise Type During Intentional Weight Loss on Body Composition in Older Adults with Obesity. Obesity (Silver Spring) 2017;25(11):1823-1829. DOI: 10.1002/oby.21977.
31. Marsh AP, Janssen JA, Ambrosius WT, et al. The Cooperative Lifestyle Intervention Program-II (CLIP-II): design and methods. Contemp Clin Trials 2013;36(2):382-93. DOI: 10.1016/j.cct.2013.08.006.