BMJ Open

Efficacy of time restricted feeding and behavioral economic interventions in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted feeding alone or usual care in patients with impaired fasting glucose: protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954
Article Type:	Protocol
Date Submitted by the Author:	03-Nov-2021
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted feeding and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted feeding alone or usual care in patients with impaired fasting glucose: protocol for a randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Corresponding author: Thunyarat Anothaisintawee, M.D., Ph.D.

Department of Family Medicine and Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

Mailing Address: Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Tel: 662-2011406

Fax: 662-2011486

Email: thunyarat.ano@mahidol.ac.th

Abstract

Introduction: Impaired fasting glucose (IFG) is a significant risk factor of diabetes mellitus (DM) and also diabetic complications. Time restricted feeding (TRF) is one type of diet that showed positive effects on many metabolic signal pathways from animal studies. However, the effects of TRF toward cardiometabolic risk factors in human are still limited. In addition, compliance of TRF remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRF with behavioral economic interventions, compared to TRF alone and usual care, in reducing fasting plasma glucose (FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel randomized controlled trial will be conducted at the outpatient clinic of Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl, and having body mass index (BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRF with behavioral economic interventions, 2) TRF alone, or 3) usual care. The duration of intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and high sensitivity C-reactive protein.

Ethics and dissemination: The study protocol have been approved by the Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389). All patients will be informed about the details of the study and sign written inform consents before enrollment to the study. Results from this study will be published in peer-reviewed journal.

Trial registration number: TCTR20210520002

Strengths and limitations of this study

- This is the first study that evaluate the effect of time restricted feeding on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The impact of behavioural economic interventions on adherence to time restricted feeding intervention will be assessed.
- The study has longer term follow up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- There may be contamination of intervention (time restricted feeding) in patients randomized to usual care group because time restricted feeding has been promoted in some social media in Thailand.

Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in Thai population is caused by DM[2]. Hence, prevention of DM in Thai population is critical to decrease further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased risk of DM in persons with IFG [4]. Most of diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted feeding (TRF) have been introduced as an alternative, which may help patients permanently maintaining their behaviors.

TRF is one type of intermittent fasting (IF) that is characterized by prolonged fasting and limited feeding time[6]. Previous literatures found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathway in animal. In human study, the TRF could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and hemoglobin A1c (HbA1c) when

compared to normal feeding style in metabolic syndrome patients[7]. Likewise, a study in obese patients also found that TRF could reduce body weight, blood pressure, low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein (HDL) cholesterol but could not reduce FPG, fasting insulin and HbA1c[8]. Contrastingly, meta-analyses found beneficial of TRF in lowering not only a body weight but also FPG, blood pressure and triglyceride levels[9 10]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRF in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRF in 15 men at risk for type 2 DM found that both early and delayed TRF improved glycemic response, but only early TRF could lower mean FPG in men with high risk of DM[11]. Another RCT assessed the effect of early TRF in 8 prediabetic men and found that early TRF could reduce insulin level, blood pressure and food appetite, increased insulin sensitivity and beta-cell responsiveness but not for FPG[12]. However, these RCT focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the long-term effect of TRF in both male and female patients is still needed.

Although TRF may have positive effects on cardiometabolic risk factors but the long-term adherence to the TRF is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desire, happens immediately. Thus, some people who place much greater weight on the present than the future will be less likely to adhere to the diet control. This is called present bias from behavioral economics perspective[13 14].

Behavioral economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[15-17]. It has gained increased

attention in promoting healthy behaviors, such as healthy food choice[18-20], physical activity[20 21], smoking cessation[20 22 23], and reduced alcohol consumption[20 24]. While conventional economics assumes rational/quantitative informed decision making, yet in reality, irrational health behaviors including overeating are common[14 16 25]. In contrast, behavioral economics accounts for irrational behaviors, perspective, or bias in explaining and predicting behavior[13 16 25].

A few behavioral economics tools have been used to deal with present bias to promote adherence to diet control, i.e., financial incentives and text reminder[26]. Previous studies show that financial incentive was an effective tool to promote healthy lifestyle such as smoking cessation and physical activity by providing immediate benefits if clients could achieve a pre-specified goal from adherence rather than letting them wait only for the intangible future health benefits[27]. In addition, findings from RCT also suggest the efficacy of financial incentive in decreasing body weight in obesity subjects[28].

Text reminder about individual's own commitment, performance, or goal (e.g., "Your goal is to stick to the TRF plan for 5 days a week.") or desired behavior can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[29], weight loss[30 31] and medication adherence[32]. An evidence of a RCT showed that text reminder was effective in improving adherence to a healthy diet and medication and could be a promising strategy for attaining permanent adherence to healthy behavior in different chronic disease[33]. As a result, using behavioral economics might be helpful in increasing compliance of lifestyle modification such as TRF or even maintaining behavioral change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle in prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRF with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to compare the efficacy of additional behavioral economic interventions in TRF to TRF alone and usual care in IFG patients with following objectives: First, to compare FPG and HbA1c levels between IFG patients who receive behavioral economic interventions plus TRF, TRF alone, and usual care. Second, to compare body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and high sensitivity C-reactive protein (hs-CRP) between these three interventions.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method is complied with the Consolidated Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Patient recruitment

Patients and staffs of Ramathibodi Hospital who are diagnosed as IFG will be recruited during October 2021 to October 2022, and they will be followed up until the 12th week after received interventions. Trained investigators and research assistants will approach and inform patients about study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Participants

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3) body mass index ≥ 25 kg/m^2. Patients will be ineligible if 1) they have been involved with Ketogenic or vegetarian diets, 2) doing night shift work at least ≥ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomizations

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRF, TRF alone, usual care with a ratio 1:1:1. A block randomization with varying block sizes of 6 and 9 will be generated by a Biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). Random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

Participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and biostatistician will be blinded about the intervention allocation. In addition, outcomes of this study will be objectively measured that will not be affected by unblinded intervention.

Study interventions

Interested interventions are TRF and behavioural economic interventions. TRF is a limitation of the daily time of food intakes to 9 hours with prolong fasting in the night-time of 15 hours. Participants will be requested to limit their periods of food intakes from 8:00 AM to 5:00 PM without restriction of types of food and beverages. Participants will be asked for complying with TRF as much as they can or at least five days per week.

Behavioural economic interventions will consist of financial incentives and text reminder. For financial incentive, participant will receive a monetary compensation of 1000 Bath per month if they can adhere to TRF at least 5 days/week. TRF adherence will be evaluated every week by asking participants record their first and last mealtime every day via logbook and financial incentive will be provided at 4th, 8th, and 12th week after randomisation. In addition, text reminder will be sent to participants every 2 days to remind them about their own commitment, performance, and goal (e.g., "Your goal is to stick to the TRF plan for at least 5 days a week", "Last week you have successfully sticked to the TRF plan for 5 days") and also about the TRF interval (e.g., "It's almost 5 pm. Let's be patient until the morning for our good health", "It's 8 AM. Well done! You gave yourself good care.").

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, exercise to prevent disease progression. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcomes of this study are FPG and HbA1c levels which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose

and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP).

Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP). Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Co-variables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives

5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Inde [34], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[35]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[36]
7. Details of food intakes assessed by 24-hour food recall
8. Time and risk preference assessed by multiple price list method[37-42]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will explained about the study protocol, process of data collection, and detail of TRF, behavioural economic interventions, and comparator. At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRF, TRF alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study).

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital number will be encrypted and keep confidentiality, unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRF and TRF alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 117 participants with 39 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage) for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRF with behavioral economic interventions and TRF alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRF plus behavioral economic interventions and TRF alone who do not comply with TRF (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRF 5 days of more per week will be excluded from analysis.

All analyses will be performed using STATA 17.0. P value of less than 0.05 will be considered as a statistical significance.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study. Protocol amendments will be reported to the institutional ethics committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. However, long term adherence to this diet control was very low. TRF is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRF on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assess the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRF intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are objectively measured, thus measurement or ascertainment bias should be less likely. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FBG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRF on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Fourth, there may be contamination of TRF in patients randomized to usual care group because TRF has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRF by themselves and this may dilute the effect of TRF in our study. We hope that this contamination should be minimized because we

will carefully assess patients who may have already performed TRF before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct an opened labeled randomized controlled trial to evaluate the efficacy of behavioral economic interventions plus TRF, TRF alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioral economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Authors' contributions: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding statement: This work was supported by National Research Council of Thailand grant number 186/2564

Competing interest statement: none

References

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530
2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14
3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025
4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]
5. 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 [published Online First: 2007/04/07]
6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]
7. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]

8. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]

9. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.

10. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]

11. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

12. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]

13. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]

14. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]

15. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]

16. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

17. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

18. Downs JS, Loewenstein G, Wisdom J. Strategies for Promoting Healthier Food Choices. *Am Econ Rev* 2009;99(2):159-64. doi: 10.1257/aer.99.2.159

19. Roberto CA, Kawachi I. Use of psychology and behavioral economics to promote healthy eating. *American journal of preventive medicine* 2014;47(6):832-37. doi: 10.1016/j.amepre.2014.08.002 [published Online First: 2014/10/18]

20. Blaga OM, Vasilescu L, Chereches RM. Use and effectiveness of behavioural economics in interventions for lifestyle risk factors of non-communicable diseases: a systematic review with policy implications. *Perspect Public Health* 2018;138(2):100-10. doi: 10.1177/1757913917720233 [published Online First: 2017/07/18]

21. Zimmerman FJ. Using behavioral economics to promote physical activity. *Prev Med* 2009;49(4):289-91. doi: https://doi.org/10.1016/j.ypmed.2009.07.008

22. Giné X, Karlan D, Zinman J. Put Your Money Where Your Butt Is: A Commitment Contract for Smoking Cessation. *American Economic Journal: Applied Economics* 2010;2(4):213-35. doi: 10.1257/app.2.4.213

23. Volpp KG, Troxel AB, Pauly MV, et al. A Randomized, Controlled Trial of Financial Incentives for Smoking Cessation. *New England Journal of Medicine* 2009;360(7):699-709. doi: 10.1056/NEJMsa0806819

24. MacKillop J. The Behavioral Economics and Neuroeconomics of Alcohol Use Disorders. *Alcohol Clin Exp Res* 2016;40(4):672-85. doi: 10.1111/acer.13004 [published Online First: 2016/03/19]

25. Volpp KG, Asch DA. Make the healthy choice the easy choice: using behavioral economics to advance a culture of health. *QJM* 2017;110(5):271-75. doi: 10.1093/qjmed/hcw190

26. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

27. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

28. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

29. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

30. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

31. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

32. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

33. Akhu-Zaheya LM, Shiyab WY. The effect of short message system (SMS) reminder on adherence to a healthy diet, medication, and cessation of smoking among adult patients with cardiovascular diseases. *Int J Med Inform* 2017;98:65-75. doi: 10.1016/j.ijmedinf.2016.12.003 [published Online First: 2016/12/31]

34. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

35. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

36. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

37. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

38. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

39. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

40. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

41. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

42. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Table 1. Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRF with economic behavioural intervention		√	√	√	√
- TRF		√	√	√	√
- Usual care		√	√	√	√
Assessment					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
Primary outcomes					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
Secondary outcomes					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

BMJ Open

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Feb-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Corresponding author: Thunyarat Anothaisintawee, M.D., Ph.D.

Department of Family Medicine and Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

Mailing Address: Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Tel: 662-2011406

Fax: 662-2011486

Email: thunyarat.ano@mahidol.ac.th

Abstract

Introduction: Impaired fasting glucose (IFG) is a significant risk factor of diabetes mellitus (DM) and also diabetic complications. Time restricted eating (TRE) is one type of diet that showed positive effects on many metabolic signal pathways from animal studies. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose (FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel randomized controlled trial will be conducted at the outpatient clinic of Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl, and having body mass index (BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The duration of intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

Ethics and dissemination: The study protocol has been approved by the Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

journal.

Trial registration number: TCTR20210520002 (18 January 2022, version 2)

Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in usual care group might be occurred due to the promoting of time restricted eating in some social media in Thailand.

Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in Thai population is caused by DM[2]. Hence, prevention of DM in Thai population is critical to decrease further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased risk of DM in persons with IFG [4]. Most of diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintaining their behaviors.

TRE is one type of dietary approaches that limits daily eating window to commonly lower than 10 h/day and prolong fasting time[6-8]. Previous literatures found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathway in animal. In human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and hemoglobin

A1c (HbA1c) when compared to normal eating style in metabolic syndrome patients[9]. Likewise, a study in obese patients also found that TRE could reduce body weight, blood pressure, low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein (HDL) cholesterol but could not reduce FPG, fasting insulin and HbA1c[10], while study of Schroder et al found the significant reduction of body mass index, body fat percentage, and waist circumference in obese middle-aged women receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different between TRE and control groups[11]. Contrastingly, meta-analyses found beneficial of TRE in lowering not only a body weight but also FPG, blood pressure and triglyceride levels[12 13]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved glycemic response, but only early TRE could lower mean FPG in men with high risk of DM[14]. Another RCT assessed the effect of early TRE in 8 prediabetic men and found that early TRE could reduce insulin level, blood pressure and food appetite, increased insulin sensitivity and beta-cell responsiveness but not for FPG[15]. However, these RCT focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the long-term effect of TRE in both male and female patients is still needed.

Although several studies found that TRE was well accepted by study's participants[16] and well tolerated even in older adults[17] but the long-term adherence to the TRE is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desire, happens immediately. Thus, some people who place much greater weight on the present than the future will be less likely to adhere to the diet

control. This is called present bias from behavioral economics perspective[18 19]. Behavioral economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[20-22].

A few behavioral economics tools have been used to deal with present bias to promote adherence to diet control, i.e., financial incentives and text reminder[23]. Previous studies show that financial incentive was an effective tool to promote healthy lifestyle such as smoking cessation, physical activity [24] and weight loss[25]. Text reminders about individual's own commitment, performance, or goal can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[26], weight loss[27 28] and medication adherence[29]. As a result, using behavioral economics might be helpful in increasing compliance of lifestyle modification such as TRF or even maintaining behavioral change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle in prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRE with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to compare the efficacy of additional behavioral economic interventions in TRE to TRE alone and usual care in IFG patients with following objectives: First, to compare FPG and HbA1c levels between IFG patients who receive behavioral economic interventions plus TRE, TRE alone, and usual care. Second, to compare body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between these three interventions.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method is complied with the Consolidated Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Patient recruitment

Patients and staffs of Ramathibodi Hospital who are diagnosed as IFG will be recruited during October 2021 to October 2022, and they will be followed up until the 12th week after received interventions. Trained investigators and research assistants will approach and inform patients about study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Participants

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3) body mass index $\geq$ 25 kg/m^2. Patients will be ineligible if 1) they have been involved with Ketogenic or vegetarian diets, 2) doing night shift work at least $\geq$ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomizations

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRE, TRE alone, usual care with a ratio 1:1:1. A block

randomization with varying block sizes of 6 and 9 will be generated by a Biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). Random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

Participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and biostatistician will be blinded about the intervention allocation. In addition, outcomes of this study will be objectively measured that will not be affected by unblinded intervention.

Study interventions

Interested interventions are TRE and behavioural economic interventions. TRE is a limitation of the daily time of food intakes to 9 hours with prolong fasting in the night-time of 15 hours. Participants will be requested to limit their periods of food intakes from 8:00 AM to 5:00 PM without restriction of types of food and beverages. Participants will be asked for complying with TRE as much as they can.

Behavioural economic interventions will consist of financial incentives and text reminder. For financial incentive, participant will receive a monetary compensation of 1000 Bath per month if they self-report that they can adhere to TRE at least 5 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants to record their first and last mealtime every day via logbook and financial incentive will be provided at 4th, 8th, and 12th week after randomisation. In addition, text reminder will be sent to participants every 2 days to remind them about their own commitment (Your goal is to stick to the TRE

plan for at least 5 days a week.), performance (Last week you have successfully sticked to the TRE plan for 5 days.), and also about the TRE interval.

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, exercise to prevent disease progression. Participants in TRF and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcomes of this study are FPG and HbA1c levels which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP).

Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Co-variables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives
5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index[30], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[31]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[32]
7. Details of food and caloric intakes assessed by 24-hour food recall and food frequency questionnaires (FFQs)
8. Time and risk preference assessed by multiple price list method[33-38]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will explained about the study protocol, process of data collection, and detail of TRE, behavioural

economic interventions, and comparator. At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study).

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital number will be encrypted and keep confidentiality, unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these

will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRE and TRE alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 114 participants with 38 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage) for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRE 5 days of more per week will be excluded from analysis.

All analyses will be performed using STATA 17.0. P value of less than 0.05 will be considered as a statistical significance.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study (see Supplementary Appendix). Protocol amendments will be reported to the institutional ethics committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Patient and Public Involvement

There was no patient or public involvement in the study.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assess the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are objectively measured, thus measurement or ascertainment bias should be less likely. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FBG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we hope that these contaminations should be minimized because we will carefully assess patients who may have already performed TRE before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct an opened labeled randomized controlled trial to evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioral economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Authors' contributions: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding statement: This work was supported by National Research Council of Thailand grant number 186/2564. The funder has no role in this study.

Competing interest statement: none

References

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530

2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14

3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025

4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]

5. 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 [published Online First: 2007/04/07]

6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]

7. Schuppelius B, Peters B, Ottawa A, et al. Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Front Endocrinol (Lausanne)*

2021;12:683140. doi: 10.3389/fendo.2021.683140 [published Online First: 2021/08/31]

8. Manoogian ENC, Zadourian A, Lo HC, et al. Protocol for a randomised controlled trial on the feasibility and effects of 10-hour time-restricted eating on cardiometabolic disease risk among career firefighters doing 24-hour shift work: the Healthy Heroes Study. *BMJ Open* 2021;11(6):e045537. doi: 10.1136/bmjopen-2020-045537 [published Online First: 2021/06/18]
9. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]
10. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]
11. Schroder JD, Falqueto H, Mânica A, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021;19(1):3. doi: 10.1186/s12967-020-02687-0
12. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.
13. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]

14. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

15. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]

16. Kesztyüs D, Cermak P, Gulich M, et al. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients* 2019;11(12):2854. doi: 10.3390/nu11122854

17. Lee SA, Sypniewski C, Bensadon BA, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients* 2020;12(3):874. doi: 10.3390/nu12030874

18. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]

19. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]

20. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]

21. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

22. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

23. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

24. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

25. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

26. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

27. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

28. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

29. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

30. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

31. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

32. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

33. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

34. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

35. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

36. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

37. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

38. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Table 1. Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
Assessment					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
Primary outcomes					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
Secondary outcomes					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

Patient/Participant Information Sheet

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name: Dr. Unyaporn Suthutvoravut

Research location: Ramathibodi Hospital Mahidol University

Who and how to contact when there is an emergency or disorder associated with research:
Dr. Unyaporn Suthutvoravut Tel. 0869041556
Dr. Thunyarat Anothaisintawee Tel. 0813725424

Sponsor for this research: National Research Council of Thailand

Project Background
Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.
Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food
Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.
Objective
To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care
Details to be treated with research participants
After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits. physical activity level together with physical examination by research assistant There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

Benefits to the research participants

Participants will gain knowledge about diet to prevent future diabetes risk.

Side effects for the participants

There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the measures given are only recommendations for time retricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

Confidentiality

The data will be collected with confidentiality. No name of number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544

Informed Consent Form

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant……

Age……medical record number……

Research Participant Consent

I, Mr./Mrs./Ms…… have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed……

(Research participant)

……..

(witness)

……..

(witness)

Date ……

Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed……

(Doctor or Researcher)

date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____3_____
Funding	4	Sources and types of financial, material, and other support	___16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 16_____
	5b	Name and contact information for the trial sponsor	____16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8-9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8-9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11-13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____-_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Apr-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Corresponding author: Thunyarat Anothaisintawee, M.D., Ph.D.

Department of Family Medicine and Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

Mailing Address: Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Tel: 662-2011406

Fax: 662-2011486

Email: thunyarat.ano@mahidol.ac.th

Abstract

Introduction: Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

Ethics and dissemination: The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

journal.

Trial registration number: TCTR20210520002 (18 January 2022, version 2) from Thai Clinical Trial Registry (TCTR) (https://thaiclinicaltrials.org)

Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM[2]. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG [4]. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time[6-8]. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and

hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with metabolic syndrome[9]. Likewise, a study in patients with obesity also found that TRE could reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and HbA1c[10], while the study of Schroder et al found the significant reduction of body mass index, body fat percentage, and waist circumference in middle-aged women with obesity receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different between TRE and control groups[11]. Contrastingly, meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood pressure, and triglyceride levels[12,13]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved glycemic response, but only early TRE could lower mean FPG in men with a high risk of DM[14]. Another RCT assessed the effect of early TRE in 8 men with prediabetes and found that early TRE could reduce insulin level, blood pressure, and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not reduce FPG[15]. However, these RCTs focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of TRE in both male and female patients is still needed.

Although several studies found that TRE was well accepted by study participants[16] and well-tolerated even in older adults[17] but the long-term adherence to TRE is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desired, happens immediately. Thus, some people who place much greater

weight on the present than on the future will be less likely to adhere to diet control. This is called present bias from behavioral economics perspective[18 19]. Behavioral economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[20-22].

A few behavioral economics tools have been used to deal with a present bias to promote adherence to diet control, i.e., financial incentives and text reminder[23]. Previous studies show that financial incentive was an effective tool to promote a healthy lifestyle such as smoking cessation, physical activity[24], and weight loss[25]. Text reminders about an individual commitment, performance, or goal can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[26], weight loss[27 28], and medication adherence[29]. As a result, using behavioral economics might help increase compliance with lifestyle modification such as TRE or even maintaining behavioral change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRE with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to compare the efficacy of additional behavioral economic interventions in TRE to TRE alone and usual care in patients with IFG with the following objectives: First, to compare FPG and HbA1c levels between patients with IFG who receive behavioral economic interventions plus TRE, TRE alone, and usual care. Second, to compare body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between these three interventions.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Patient recruitment

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12th week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Participants

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with or without HbA1c of 5.7-6.49%, and 3) body mass index $\geq$ 25 kg/m^2. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least $\geq$ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomizations

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block

randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

Participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and a biostatistician will be blinded about the intervention allocation. In addition, the outcomes of this study will be objectively measured that will not be affected by the unblinded intervention.

Study interventions

Interested interventions are TRE and behavioural economic interventions. TRE is a limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM to 5:00 PM without restriction on types of food and beverages. Participants will be asked for complying with TRE as much as they can.

Behavioural economic interventions will consist of financial incentives and text reminders. For financial incentive, the participant will receive monetary compensation of 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants to record their first and last mealtime every day via logbook and financial incentives will be provided on 4^{th}, 8^{th}, and 12^{th} week after randomisation. In addition, text reminders will be sent to participants every 2 days to remind them about their commitment (Your goal is to stick to the TRE plan for at least 5 days a week.), performance (Last week you have

successfully sticked to the TRE plan for 5 days.), and also about the TRE interval. The TRE alone group will be advised about the benefit of TRE without any additional support. However, the participants in TRE alone group will be asked to record the adherence of TRE via logbook.

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcomes of this study are FPG and HbA1c levels which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP).

Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent

microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Co-variables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives
5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index[30], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[31]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[32]
7. Details of food and caloric intakes assessed by 24-hour food recall and food frequency questionnaires (FFQs)
8. Time and risk preference assessed by multiple price list method[33-38]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study). 24-hour food recall will be collected using food diary for 7 days at each visit. INMUCAL-nutrients version 4.0 (https://inmu2.mahidol.ac.th/inmucal/index.php) will be used to calculate the dietary data to nutrient intakes. This program was developed by the Institute of Nutrition, Mahidol University, Thailand.

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will

be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital numbers will be encrypted and kept confidentiality; unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRE and TRE alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 114 participants with 38 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage) for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention

and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRE 5 days of more per week will be excluded from analysis. Multivariate linear regression analysis will be applied, if there is the difference in baseline characteristics between 3 groups.

All analyses will be performed using STATA 17.0. P value of less than 0.05 will be considered as a statistical significance.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study (see Supplementary Appendix). Protocol amendments will be reported to the institutional ethics committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Patient and Public Involvement

There was no patient or public involvement in the study.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we

hope that these contaminations should be minimized because we will carefully assess patients who may have already performed TRE before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct an opened labeled randomized controlled trial to evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioral economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Authors' contributions: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding statement: This work was supported by National Research Council of Thailand grant number 186/2564. The funder has no role in this study.

Competing interest statement: none

References

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530

2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14

3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025

4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]

5. 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 [published Online First: 2007/04/07]

6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]

7. Schuppelius B, Peters B, Ottawa A, et al. Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Front Endocrinol (Lausanne)*

2021;12:683140. doi: 10.3389/fendo.2021.683140 [published Online First: 2021/08/31]

8. Manoogian ENC, Zadourian A, Lo HC, et al. Protocol for a randomised controlled trial on the feasibility and effects of 10-hour time-restricted eating on cardiometabolic disease risk among career firefighters doing 24-hour shift work: the Healthy Heroes Study. *BMJ Open* 2021;11(6):e045537. doi: 10.1136/bmjopen-2020-045537 [published Online First: 2021/06/18]
9. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]
10. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]
11. Schroder JD, Falqueto H, Mânica A, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021;19(1):3. doi: 10.1186/s12967-020-02687-0
12. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.
13. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]

14. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

15. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]

16. Kesztyüs D, Cermak P, Gulich M, et al. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients* 2019;11(12):2854. doi: 10.3390/nu11122854

17. Lee SA, Sypniewski C, Bensadon BA, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients* 2020;12(3):874. doi: 10.3390/nu12030874

18. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]

19. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]

20. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]

21. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

22. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

23. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

24. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

25. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

26. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

27. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

28. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

29. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

30. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

31. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

32. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

33. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

34. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

35. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

36. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

37. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

38. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Table 1. Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
Assessment					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
Primary outcomes					

- FPG		√	√	√	√
- HbA1c		√	√	√	√
Secondary outcomes					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

Patient/Participant Information Sheet

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name: Dr. Unyaporn Suthutvoravut

Research location: Ramathibodi Hospital Mahidol University

Who and how to contact when there is an emergency or disorder associated with research:
Dr. Unyaporn Suthutvoravut Tel. 0869041556
Dr. Thunyarat Anothaisintawee Tel. 0813725424

Sponsor for this research: National Research Council of Thailand

Project Background
Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.
Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food
Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.
Objective
To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care
Details to be treated with research participants
After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits. physical activity level together with physical examination by research assistant There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

Benefits to the research participants

Participants will gain knowledge about diet to prevent future diabetes risk.

Side effects for the participants

There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the measures given are only recommendations for time retricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

Confidentiality

The data will be collected with confidentiality. No name of number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544

Informed Consent Form

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant……

Age……medical record number……

Research Participant Consent

I, Mr./Mrs./Ms…… have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed……

(Research participant)

……..

(witness)

……..

(witness)

Date ……

Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed……

(Doctor or Researcher)

date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____3_____
Funding	4	Sources and types of financial, material, and other support	___16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 16_____
	5b	Name and contact information for the trial sponsor	____16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8-9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8-9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11-13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____-_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954.R3
Article Type:	Protocol
Date Submitted by the Author:	24-May-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Corresponding author: Thunyarat Anothaisintawee, M.D., Ph.D.

Department of Family Medicine and Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

Mailing Address: Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Tel: 662-2011406

Fax: 662-2011486

Email: thunyarat.ano@mahidol.ac.th; thunyarata@gmail.com

Abstract

Introduction: Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions, compared to TRE alone and usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcomes are FPG and HbA1c levels measured at 12 weeks after randomization. Secondary outcomes are body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

Ethics and dissemination: The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

journal.

Trial registration number: TCTR20210520002 (18 January 2022, version 2) from Thai Clinical Trial Registry (TCTR) (https://thaiclinicaltrials.org)

Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM[2]. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG [4]. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time[6-8]. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and

hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with metabolic syndrome[9]. Likewise, a study in patients with obesity also found that TRE could reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and HbA1c[10], while the study of Schroder et al found the significant reduction of body mass index, body fat percentage, and waist circumference in middle-aged women with obesity receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different between TRE and control groups[11]. Contrastingly, meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood pressure, and triglyceride levels[12,13]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved glycemic response, but only early TRE could lower mean FPG in men with a high risk of DM[14]. Another RCT assessed the effect of early TRE in 8 men with prediabetes and found that early TRE could reduce insulin level, blood pressure, and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not reduce FPG[15]. However, these RCTs focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of TRE in both male and female patients is still needed.

Although several studies found that TRE was well accepted by study participants[16] and well-tolerated even in older adults[17] but the long-term adherence to TRE is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desired, happens immediately. Thus, some people who place much greater

weight on the present than on the future will be less likely to adhere to diet control. This is called present bias from behavioral economics perspective[18 19]. Behavioral economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[20-22].

A few behavioral economics tools have been used to deal with a present bias to promote adherence to diet control, i.e., financial incentives and text reminder[23]. Previous studies show that financial incentive was an effective tool to promote a healthy lifestyle such as smoking cessation, physical activity[24], and weight loss[25]. Text reminders about an individual commitment, performance, or goal can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[26], weight loss[27 28], and medication adherence[29]. As a result, using behavioral economics might help increase compliance with lifestyle modification such as TRE or even maintaining behavioral change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRE with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to compare the efficacy of additional behavioral economic interventions in TRE to TRE alone and usual care in patients with IFG with the following objectives: First, to compare FPG and HbA1c levels between patients with IFG who receive behavioral economic interventions plus TRE, TRE alone, and usual care. Second, to compare body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between these three interventions.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Patient recruitment

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12th week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Participants

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body mass index $\geq$ 25 kg/m^2. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least $\geq$ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomizations

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block

randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

Participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and a biostatistician will be blinded about the intervention allocation. In addition, the outcomes of this study will be objectively measured that will not be affected by the unblinded intervention.

Study interventions

Interested interventions are TRE and behavioural economic interventions. TRE is a limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM to 5:00 PM without restriction on types of food and beverages. Participants will be asked for complying with TRE as much as they can.

Behavioural economic interventions will consist of financial incentives and text reminders. For financial incentive, the participant will receive monetary compensation of 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants to record their first and last mealtime every day via logbook and financial incentives will be provided on 4^{th}, 8^{th}, and 12^{th} week after randomisation. In addition, text reminders will be sent to participants every 2 days to remind them about their commitment (Your goal is to stick to the TRE plan for at least 5 days a week.), performance (Last week you have

successfully sticked to the TRE plan for 5 days.), and also about the TRE interval. The TRE alone group will be advised about the benefit of TRE without any additional support. However, the participants in TRE alone group will be asked to record the adherence of TRE via logbook.

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcomes of this study are FPG and HbA1c levels which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose and HbA1c will be measured by hexokinase glucose-6 phosphate dehydrogenase and turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP).

Secondary outcomes are body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent

microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Co-variables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives
5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index[30], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[31]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[32]
7. Details of food and caloric intakes assessed by 24-hour food recall and food frequency questionnaires (FFQs)
8. Time and risk preference assessed by multiple price list method[33-38]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study). 24-hour food recall will be collected using food diary for 7 days at each visit. INMUCAL-nutrients version 4.0 (https://inmu2.mahidol.ac.th/inmucal/index.php) will be used to calculate the dietary data to nutrient intakes. This program was developed by the Institute of Nutrition, Mahidol University, Thailand.

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will

be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital numbers will be encrypted and kept confidentiality; unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRE and TRE alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 114 participants with 38 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage) for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention

and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRE 5 days of more per week will be excluded from analysis. Multivariate regression analysis will be applied, if there is the difference in baseline characteristics between 3 groups.

All analyses will be performed using STATA 17.0. P value of less than 0.05 will be considered as a statistical significance.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study (see Supplementary Appendix). Protocol amendments will be reported to the institutional ethics committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Patient and Public Involvement

There was no patient or public involvement in the study.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we

hope that these contaminations should be minimized because we will carefully assess patients who may have already performed TRE before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct an opened labeled randomized controlled trial to evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioral economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Authors' contributions: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding statement: This work was supported by National Research Council of Thailand grant number 186/2564. The funder has no role in this study.

Competing interest statement: none

References

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530

2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14

3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025

4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]

5. 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 [published Online First: 2007/04/07]

6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]

7. Schuppelius B, Peters B, Ottawa A, et al. Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Front Endocrinol (Lausanne)*

2021;12:683140. doi: 10.3389/fendo.2021.683140 [published Online First: 2021/08/31]

8. Manoogian ENC, Zadourian A, Lo HC, et al. Protocol for a randomised controlled trial on the feasibility and effects of 10-hour time-restricted eating on cardiometabolic disease risk among career firefighters doing 24-hour shift work: the Healthy Heroes Study. *BMJ Open* 2021;11(6):e045537. doi: 10.1136/bmjopen-2020-045537 [published Online First: 2021/06/18]
9. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]
10. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]
11. Schroder JD, Falqueto H, Mânica A, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021;19(1):3. doi: 10.1186/s12967-020-02687-0
12. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.
13. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]

14. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

15. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]

16. Kesztyüs D, Cermak P, Gulich M, et al. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients* 2019;11(12):2854. doi: 10.3390/nu11122854

17. Lee SA, Sypniewski C, Bensadon BA, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients* 2020;12(3):874. doi: 10.3390/nu12030874

18. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]

19. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]

20. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]

21. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

22. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

23. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

24. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

25. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

26. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

27. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

28. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

29. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

30. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

31. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

32. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

33. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

34. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

35. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

36. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

37. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

38. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Table 1. Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
Assessment					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√

- Time and risk preference		√			√
Primary outcomes					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
Secondary outcomes					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

Patient/Participant Information Sheet

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name: Dr. Unyaporn Suthutvoravut

Research location: Ramathibodi Hospital Mahidol University

Who and how to contact when there is an emergency or disorder associated with research:
Dr. Unyaporn Suthutvoravut Tel. 0869041556
Dr. Thunyarat Anothaisintawee Tel. 0813725424

Sponsor for this research: National Research Council of Thailand

Project Background
Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.
Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food
Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.
Objective
To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care
Details to be treated with research participants
After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits. physical activity level together with physical examination by research assistant There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

Benefits to the research participants

Participants will gain knowledge about diet to prevent future diabetes risk.

Side effects for the participants

There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the measures given are only recommendations for time retricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

Confidentiality

The data will be collected with confidentiality. No name of number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544

Informed Consent Form

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant……

Age……medical record number……

Research Participant Consent

I, Mr./Mrs./Ms…… have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed……

(Research participant)

……..

(witness)

……..

(witness)

Date ……

Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed……

(Doctor or Researcher)

date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____3_____
Funding	4	Sources and types of financial, material, and other support	___16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 16_____
	5b	Name and contact information for the trial sponsor	____16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8-9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8-9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11-13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____-_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954.R4
Article Type:	Protocol
Date Submitted by the Author:	04-Aug-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Corresponding author: Thunyarat Anothaisintawee, M.D., Ph.D.

Department of Family Medicine and Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University

Mailing Address: Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Tel: 662-2011406

Fax: 662-2011486

Email: thunyarat.ano@mahidol.ac.th; thunyarata@gmail.com

Abstract

Introduction: Impaired fasting glucose(IFG) is a significant risk factor for diabetes mellitus(DM). Time restricted eating(TRE) is one type of diet that showed positive effects on many metabolic signal pathways. However, the effects of TRE on cardiometabolic risk factors in humans are still limited. In addition, compliance with TRE remains problematic for some people despite their intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioral economic interventions or TRE alone relative to usual care, in reducing fasting plasma glucose(FPG), hemoglobin A1c(HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and having body mass index(BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioral economic interventions which include financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcome is FPG levels measured at 12 weeks after randomization. Secondary outcomes are HbA1c, body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein.

Ethics and dissemination: The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University(MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrollment in the study. Results from this study will be published in peer-reviewed

journal.

Trial registration number: TCTR20210520002 (18 January 2022, version 2) from Thai Clinical Trial Registry (TCTR) (https://thaiclinicaltrials.org)

Strengths and limitations of this study

- First randomized controlled trial that assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might be occurred due to the promotion of time restricted eating on some social media in Thailand.

Background and rationale

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM[2]. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG [4]. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviors or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviors.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time[6-8]. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and

hemoglobin A1c (HbA1c) when compared to the normal eating style in patients with metabolic syndrome[9]. Likewise, a study in patients with obesity also found that TRE could reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and HbA1c[10], while the study of Schroder et al found the significant reduction of body mass index, body fat percentage, and waist circumference in middle-aged women with obesity receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different between TRE and control groups[11]. Contrastingly, meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood pressure, and triglyceride levels[12,13]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved glycemic response, but only early TRE could lower mean FPG in men with a high risk of DM[14]. Another RCT assessed the effect of early TRE in 8 men with prediabetes and found that early TRE could reduce insulin level, blood pressure, and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not reduce FPG[15]. However, these RCTs focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of TRE in both male and female patients is still needed.

Although several studies found that TRE was well accepted by study participants[16] and well-tolerated even in older adults[17] but the long-term adherence to TRE is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desired, happens immediately. Thus, some people who place much greater

weight on the present than on the future will be less likely to adhere to diet control. This is called present bias from behavioral economics perspective[18 19]. Behavioral economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[20-22].

A few behavioral economics tools have been used to deal with a present bias to promote adherence to diet control, i.e., financial incentives and text reminder[23]. Previous studies show that financial incentive was an effective tool to promote a healthy lifestyle such as smoking cessation, physical activity[24], and weight loss[25]. Text reminders about an individual commitment, performance, or goal can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[26], weight loss[27 28], and medication adherence[29]. As a result, using behavioral economics might help increase compliance with lifestyle modification such as TRE or even maintaining behavioral change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRE with behavioral economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to determine the efficacy of TRE plus behavioral economic interventions or TRE, when compare with usual care alone in patients with IFG with the following objectives. First, to investigate whether providing TRE plus behavioral economic interventions or TRE in addition to usual care for patients with IFG will provide additional benefit in reducing FPG when compared with usual care alone? Second, to compare HbA1c, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between these three interventions.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement extension for multi-arm trials. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Patient recruitment

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12th week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Participants

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body mass index $\geq$ 25 kg/m^2. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least $\geq$ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomizations

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

Participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and a biostatistician will be blinded about the intervention allocation. In addition, the outcomes of this study will be objectively measured that will not be affected by the unblinded intervention.

Study interventions

Interested interventions are TRE and behavioural economic interventions. TRE is a limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM to 5:00 PM without restriction on types of food and beverages. Participants will be asked for complying with TRE as much as they can.

Behavioural economic interventions will consist of financial incentives and text reminders. For financial incentive, the participant will receive monetary compensation of 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants to record their first and last mealtime every day via logbook and financial incentives will be provided on 4^{th}, 8^{th}, and 12^{th} week after randomisation. In addition, text reminders will be

sent to participants every 2 days to remind them about their commitment (Your goal is to stick to the TRE plan for at least 5 days a week.), performance (Last week you have successfully sticked to the TRE plan for 5 days.), and also about the TRE interval. The TRE alone group will be advised about the benefit of TRE without any additional support. However, the participants in TRE alone group will be asked to record the adherence of TRE via logbook.

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcome of this study is FPG which will be measured at the end of the study, i.e., 3 months after randomisation. Fasting plasma glucose will be measured by hexokinase glucose-6 phosphate dehydrogenase.

Secondary outcomes are HbA1c, body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. HbA1c will be measured by turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP). Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an

automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Co-variables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives
5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index[30], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[31]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[32]
7. Details of food and caloric intakes assessed by 24-hour food recall and food frequency questionnaires (FFQs)
8. Time and risk preference assessed by multiple price list method[33-38]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study). 24-hour food recall will be collected using food diary for 7 days at each visit. INMUCAL-nutrients version 4.0 (https://inmu2.mahidol.ac.th/inmucal/index.php) will be used to calculate the dietary data to nutrient intakes. This program was developed by the Institute of Nutrition, Mahidol University, Thailand.

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital numbers will be encrypted and kept confidentiality; unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRE and TRE alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 114 participants with 38 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage)

for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRE with behavioral economic interventions and TRE alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly. Sensitivity analysis will be performed to check the robustness of the primary analyses. Independent T-test will be applied to compare means of primary and secondary outcomes at the end of the study between TRE plus behavioural economic interventions and usual care groups and to compare mean of primary and secondary outcomes between TRE and usual care groups. Last observation carried forward (LOCF) will be applied to impute the missing outcome data for patients who are loss to follow up.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRE plus behavioral economic interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRE 5 days of more per week will be excluded from analysis. Multivariate regression analysis will be applied, if there is the difference in baseline characteristics between 3 groups.

All analyses will be performed using STATA 17.0. P value of less than 0.05 will be considered as a statistical significance.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study (see Supplementary Appendix). Protocol amendments will be reported to the institutional ethics

committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Patient and Public Involvement

There was no patient or public involvement in the study.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot

be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out from the study. These drawbacks may dilute the effect of TRE in our study. However, we hope that these contaminations should be minimized because we will carefully assess patients who may have already performed TRE before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct an opened labeled randomized controlled trial to evaluate the efficacy of behavioral economic interventions plus TRE, TRE alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioral economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Authors' contributions: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding statement: This work was supported by National Research Council of Thailand grant number 186/2564. The funder has no role in this study.

Competing interest statement: none **References**

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530

2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14

3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025

4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]

5. 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 [published Online First: 2007/04/07]

6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]

7. Schuppelius B, Peters B, Ottawa A, et al. Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Front Endocrinol (Lausanne)* 2021;12:683140. doi: 10.3389/fendo.2021.683140 [published Online First: 2021/08/31]

8. Manoogian ENC, Zadourian A, Lo HC, et al. Protocol for a randomised controlled trial on the feasibility and effects of 10-hour time-restricted eating on cardiometabolic disease risk among career firefighters doing 24-hour shift work: the Healthy Heroes Study. *BMJ Open* 2021;11(6):e045537. doi: 10.1136/bmjopen-2020-045537 [published Online First: 2021/06/18]

9. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]

10. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]

11. Schroder JD, Falqueto H, Mânica A, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021;19(1):3. doi: 10.1186/s12967-020-02687-0

12. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.

13. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]

14. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover

Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

15. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]
16. Kesztyüs D, Cermak P, Gulich M, et al. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients* 2019;11(12):2854. doi: 10.3390/nu11122854
17. Lee SA, Sypniewski C, Bensadon BA, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients* 2020;12(3):874. doi: 10.3390/nu12030874
18. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]
19. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]
20. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]
21. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

22. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

23. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

24. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

25. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

26. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

27. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

28. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

29. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

30. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

31. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

32. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

33. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

34. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

35. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

36. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

37. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

38. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Table 1. Schedule matrix including activities and time at measurements/data collection

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
Assessment					
- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√

- Time and risk preference		√			√
Primary outcomes					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
Secondary outcomes					
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

Patient/Participant Information Sheet

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name: Dr. Unyaporn Suthutvoravut

Research location: Ramathibodi Hospital Mahidol University

Who and how to contact when there is an emergency or disorder associated with research:
Dr. Unyaporn Suthutvoravut Tel. 0869041556
Dr. Thunyarat Anothaisintawee Tel. 0813725424

Sponsor for this research: National Research Council of Thailand

Project Background
Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.
Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food
Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.
Objective
To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care
Details to be treated with research participants
After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits. physical activity level together with physical examination by research assistant There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

Benefits to the research participants

Participants will gain knowledge about diet to prevent future diabetes risk.

Side effects for the participants

There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the measures given are only recommendations for time retricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

Confidentiality

The data will be collected with confidentiality. No name of number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544

Informed Consent Form

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant……

Age……medical record number……

Research Participant Consent

I, Mr./Mrs./Ms…… have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed……

(Research participant)

……..

(witness)

……..

(witness)

Date ……

Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed……

(Doctor or Researcher)

date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____3_____
Funding	4	Sources and types of financial, material, and other support	___16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 16_____
	5b	Name and contact information for the trial sponsor	____16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8-9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8-9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11-13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____-_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of time restricted eating and behavioural economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared with time restricted eating alone or usual care in patients with impaired fasting glucose: protocol for an open-label randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058954.R5
Article Type:	Protocol
Date Submitted by the Author:	25-Aug-2022
Complete List of Authors:	Suthutvoravut, Unyaporn; Mahidol University, Department of Family Medicine Anothaisintawee, Thunyarat; Mahidol University, Department of Family Medicine; Mahidol University, Department of Clinical Epidemiology and Biostatistics Boonmanunt, Suparee; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Clinical Epidemiology and Biostatistics Pramyothin, Sarunporn; Mahidol University Chaithanasarn, Arthit; Mahidol University Faculty of Medicine Ramathibodi Hospital, Department of Family Medicine Reutrakul, Sirimon; University of Illinois, Department of Medicine Thakkinstian, Ammarin ; Mahidol University Faculty of Medicine Ramathibodi Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, NUTRITION & DIETETICS

Efficacy of time restricted eating and behavioural economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared with time restricted eating alone or usual care in patients with impaired fasting glucose: protocol for an open-label randomized controlled trial

Unyaporn Suthutvoravut[a], Thunyarat Anothaisintawee[a,b], Suparee Boonmanunt[b], Sarunporn Pramyothin[c], Arthit Chaithanasarn[a], Sirimon Reutrakul[d], Ammarin Thakkinstian[b]

[a]Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[b]Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[c]Medical Services Division, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[d]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago, IL 60612, USA.

Correspondence to:

Thunyarat Anothaisintawee, M.D., Ph.D., Ramathibodi Hospital, Praram VI Road, Rachathevee, Bangkok, Thailand, 10400, Thailand

Email: thunyarat.ano@mahidol.ac.th; thunyarata@gmail.com

Abstract

Introduction: Impaired fasting glucose (IFG) is a significant risk factor for diabetes mellitus (DM). Time restricted eating (TRE) is one type of diet showing positive effects on metabolic

signal pathways. However, effects of TRE on cardiometabolic risk factors in humans are limited. Additionally, compliance with TRE remains problematic despite having intention to follow the diet control. Therefore, this study aims to investigate the efficacy of TRE with behavioural economic interventions or TRE alone relative to usual care, in reducing fasting plasma glucose (FPG), haemoglobin A1c (HbA1c), and other cardiometabolic risk factors in patients with IFG.

Methods and analysis: This parallel-group, open-label randomized controlled trial will be conducted at the outpatient clinic of the Department of Family Medicine, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. Patients aged 18-65 years with IFG defined as FPG 100-125 mg/dl and body mass index (BMI) $\geq$ 25 kg/m^2 will be recruited between October 2021 and October 2022. Patients will be randomly allocated to 3 groups (1:1:1 ratio) as 1) TRE with behavioural economic interventions including financial incentives and text reminders, 2) TRE alone, or 3) usual care. The number of participants will be 38 per group (a total of 114). The duration of the intervention will be 12 weeks. Primary outcome is FPG levels measured at 12 weeks after randomization. Secondary outcomes are HbA1c, body weight, systolic and diastolic blood pressure, fasting insulin, serum triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein. P-value<0.05 of 2-sided test will be considered as statistical significance.

Ethics and dissemination: The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (MURA2021/389). All patients will be informed about the details of the study and sign written informed consent before enrolment in the study. Results from this study will be published in peer-reviewed journal.

Trial registration number: Thai Clinical Trial Registry, TCTR20210520002 (18 January 2022, version 2).

Strengths and limitations of this study

- The study uses a randomized controlled trial design to assesses the efficacy of time restricted eating on blood sugar levels and other cardiometabolic risk factors in patients with impaired fasting glucose.
- The study has longer-term follow-up than previous studies.
- The interventions cannot be blinded; hence, the results may be affected by observer and information bias.
- Contamination of time restricted eating in the usual care group might occur due to the promotion of time restricted eating on some social media in Thailand.

Introduction

Diabetes mellitus (DM) is one of the important health problems in Thailand. The results from the National health examination survey reported that the prevalence of DM in the Thai population has increased from 7.7% in 2004 to 9.9% in 2014[1]. Diabetes is a risk factor for cardiovascular diseases (CVD) and also the cause of microvascular complications such as chronic kidney disease (CKD) and diabetic retinopathy. Moreover, around 4% of mortality in the Thai population is caused by DM[2]. Hence, the prevention of DM in the Thai population is critical to decreasing further morbidity and mortality in the future.

Impaired fasting glucose (IFG) or intermediate hyperglycaemia is the condition in which blood sugar level is higher than normal but does not reach the DM threshold. A person with IFG has a higher risk for DM about 13 times than a person with a normal blood glucose level[3]. Evidence from a previous umbrella review found that lifestyle modifications by diet control and exercise significantly decreased the risk of DM in persons with IFG [4]. Most diet interventions including low and very low-calorie diets are mainly focused on caloric restriction (CR) with the main objective of body weight reduction. Although the efficacy of these diet interventions in decreasing DM risk is well established, most patients could not sustain their healthy behaviours or maintain their healthy lifestyle permanently[5]. As a result, other methods of diet control such as time restricted eating (TRE) have been introduced as an alternative, which may help patients permanently maintain their behaviours.

TRE is one type of dietary approach that limits the daily eating window to commonly lower than 10 h/day and prolongs fasting time[6-8]. Previous literature found that increased fasting time has positive effects on many metabolic signal pathways, i.e., prolonged fasting stimulated autophagy and cell repair including mitochondria biogenesis resulting in better metabolic signal pathways in animals. In a human study, the TRE could significantly lower body weight but could not decline fasting plasma glucose (FPG), fasting insulin, and

haemoglobin A1c (HbA1c) when compared to the normal eating style in patients with metabolic syndrome[9]. Likewise, a study in patients with obesity also found that TRE could reduce body weight, blood pressure, low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein (HDL-C) cholesterol but could not reduce FPG, fasting insulin and HbA1c[10], while the study of Schroder et al found the significant reduction of body mass index, body fat percentage, and waist circumference in middle-aged women with obesity receiving TRE but FPG, HbA1c, fasting insulin, LDL-C, HDL-C, serum uric acid, and blood pressure were not significantly different between TRE and control groups[11]. Contrastingly, meta-analyses found beneficial of TRE in lowering not only body weight but also FPG, blood pressure, and triglyceride levels[12,13]. Until now, there are few small randomized controlled trials (RCT) that examined the effect of TRE in patients with prediabetes. A cross-over RCT assessing the effects of early or delayed TRE in 15 men at risk for type 2 DM found that both early and delayed TRE improved glycaemic response, but only early TRE could lower mean FPG in men with a high risk of DM[14]. Another RCT assessed the effect of early TRE in 8 men with prediabetes and found that early TRE could reduce insulin level, blood pressure, and food appetite, increase insulin sensitivity and beta-cell responsiveness but could not reduce FPG[15]. However, these RCTs focused on only men with very short follow-up times (i.e., 7 days and 5 weeks). Therefore, further RCT investigating the longer-term effect of TRE in both male and female patients is still needed.

Although several studies found that TRE was well accepted by study participants[16] and well-tolerated even in older adults[17] but the long-term adherence to TRE is still questionable in the real life of some people. Such a gap occurs because the benefits of reducing cardiometabolic risks are intangible and will occur in the far future, whereas the cost of adherence to this diet control, namely being disciplined on diet time instead of eating freely whenever desired, happens immediately. Thus, some people who place much greater

weight on the present than on the future will be less likely to adhere to diet control. This is called present bias from behavioural economics perspective[18 19]. Behavioural economics is a field that integrates insights and methods from psychology and economics to understand human decision-making[20-22].

A few behavioural economics tools have been used to deal with a present bias to promote adherence to diet control, i.e., financial incentives and text reminder[23]. Previous studies show that financial incentive was an effective tool to promote a healthy lifestyle such as smoking cessation, physical activity[24], and weight loss[25]. Text reminders about an individual commitment, performance, or goal can immediately remind them of the priority. Such reminders have been proven effective in many domains, such as for the promotion of savings[26], weight loss[27 28], and medication adherence[29]. As a result, using behavioural economics might help increase compliance with lifestyle modification such as TRE or even maintaining behavioural change and finally improve the efficacy of lifestyle intervention in people with IFG who require a lifelong healthy lifestyle to prevention of DM conversion.

Nevertheless, there has been no study that assesses the efficacy of combined TRE with behavioural economic interventions in patients with IFG. Therefore, this RCT protocol is developed which aims to determine the efficacy of TRE plus behavioural economic interventions or TRE alone, when compare with usual care in patients with IFG with the following objectives. First, to investigate whether providing TRE plus behavioural economic interventions or TRE alone for patients with IFG will provide additional benefit in reducing FPG when compared with usual care? Second, to compare HbA1c, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and high sensitivity C-reactive protein (hs-CRP) between TRE plus behavioural economic interventions or TRE alone with usual care.

Methods and analysis

Study design

This study is a parallel RCT, which will be conducted at the outpatient clinic of the Department of Family Medicine (OFM), Faculty of Medicine, Ramathibodi Hospital, during October 2021 to October 2022. This research method complies with the Consolidated Standards of Reporting Trials (CONSORT) statement extension for multi-arm trials. The trial protocol has been registered at the Thai Clinical Trials Registry (TCTR20210520002).

Participants

Patients and staffs of Ramathibodi Hospital who are diagnosed with IFG will be recruited from October 2021 to October 2022, and they will be followed up until the 12th week after receiving interventions. Trained investigators and research assistants will approach and inform patients about the study protocol, randomization process, and details of intervention and comparisons. Participants will sign informed consent before participating.

Patients will be included in this study, if they meet all of the following criteria: 1) age 18 to 65 years, 2) having FPG of 100-125 mg/dl with HbA1c less than 6.5%, and 3) body mass index $\geq$ 25 kg/m^2. The Patients will be ineligible if 1) they are currently on Ketogenic or vegetarian diets, 2) doing night shift work at least $\geq$ 3 hours during 10:00 PM-5:00 AM more than 1 day/week, 3) having more than 5 kg body weight changes during the 3 months before enrolment to the study, 4) taking medicines that must be taken with food in the early morning (i.e., before 8:00 AM) or late evening (i.e., after 5:00 PM), 5) pregnancy or breastfeeding, 6) having psychiatric disorders such as eating disorder or mood disorder but not including depression, 7) taking corticosteroid or anti-diabetic drugs, 8) having a history of bariatric surgery, and 9) having impaired nutrients absorption.

Randomization

Patients will be randomly assigned to any of three interventions including behavioural economic interventions plus TRE, TRE alone, and usual care with a ratio of 1:1:1. Block randomization with varying block sizes of 6 and 9 will be generated by a biostatistician who does not involve in the trial using STATA program version 16. Randomization will be stratified according to age groups (i.e., 18-59 years and 60-65 years). A random sequence list will be then concealed using sequential opaque sealed envelopes, which will be kept at the OFM. A research assistant will administer and open the sealed envelope once patients are eligible.

Blinding

The study is open label as participants and clinicians cannot be blinded due to the nature of interventions. However, data collectors and a biostatistician will be blinded about the intervention allocation. In addition, the outcomes of this study will be objectively measured that will not be affected by the unblinded intervention.

Study interventions

Interested interventions are TRE and behavioural economic interventions. TRE is a limitation of the daily time of food intake to 9 hours with prolonged fasting in the night time of 15 hours. Participants will be requested to limit their periods of food intake from 8:00 AM to 5:00 PM without restriction on types of food and beverages. Participants will be asked for complying with TRE as much as they can.

Behavioural economic interventions will consist of financial incentives and text reminders. For financial incentive, the participant will receive monetary compensation of 1000 Baths per month (23 £) if they self-report that they can adhere to TRE at least 5 days/week for 4 weeks. TRE adherence will be evaluated every week by asking participants to record their first and last mealtime every day via logbook and financial incentives will be provided on 4^{th}, 8^{th}, and 12^{th} week after randomisation. In addition, text reminders will be

sent to participants every 2 days to remind them about their commitment (Your goal is to stick to the TRE plan for at least 5 days a week.), performance (Last week you have successfully sticked to the TRE plan for 5 days.), and also about the TRE interval. The TRE alone group will be advised about the benefit of TRE without any additional support. However, the participants in TRE alone group will be asked to record the adherence of TRE via logbook.

Comparator of the study is a usual care according to the current practice guideline of diabetes prevention. Patients will be educated about their conditions and disease progression, dietary control, and exercise to prevent disease progression. Participants in TRE and behavioural economic interventions and TRE alone groups also will receive the education about dietary control and exercise similar to patients in the usual care group. In addition, patients will be asked to record their first and last mealtime every day, which will be the same as patients in the other two interventions to evaluate protocol violation. All patients in 3 groups will received a leaflet that provides knowledge about healthy food and lifestyle modification to control their weight and reduce the risk of progression to DM.

Outcomes

The primary outcome of this study is FPG which will be measured at the end of the study, i.e., 3 months (12 weeks) after randomisation. Fasting plasma glucose will be measured by hexokinase glucose-6 phosphate dehydrogenase.

Secondary outcomes are HbA1c, body weight, SBP, DBP, fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP. HbA1c will be measured by turbid metric inhibition immunoassay certified by the National Glycohemoglobin Standardization Program (NGSP). Body weight and blood pressure measurement will be taken by trained research assistants. Body weight will be measured without shoes to the nearest 100 g. Blood pressure will measured after the resting for at least 15 minutes with an

automatic blood pressure monitoring. Fasting insulin, serum triglyceride, total cholesterol, LDL-C, HDL-C, and hs-CRP will be measured by chemiluminescent microparticle immunoassay, glycerol phosphate oxidase, enzymatic method, liquid selective detergent, accelerator selective detergent, and immunonephelometry, respectively.

All primary and secondary outcomes will be measured at the baseline, 1, 2, and 3 months after randomization.

Adverse events

Adverse events such as syncope, dizziness, and light headiness will be measured during all study periods.

Covariables

Other covariables will be collected as follows.

1. Demographic data including age, sex, educational level, and marital status
2. Underlying diseases such as hypertension, dyslipidaemia, fatty liver disease, and history of gestational diabetes mellitus
3. Health risk behaviours including smoking and alcohol intake
4. Family history of DM in the first degree relatives
5. Sleep factors including sleep duration, sleep quality measured by the Thai version of the Pittsburgh Sleep Quality Index[30], and morningness and eveningness preference using the validated Thai version of the Composite Scale of Morningness (CSM)[31]
6. Physical activity level measured by Global Physical Activity Questionnaire (GPAQ)[32]
7. Details of food and caloric intakes assessed by 24-hour food recall and food frequency questionnaires (FFQs)
8. Time and risk preference assessed by multiple price list method[33-38]

Study protocol and data collection

Schedule matrix consisting of data collections and time at measurements are presented in Table 1. At the first visit, trained investigator and research assistants will recruit the patient by screening FPG and other inclusion criteria (i.e., age and BMI). If the patient meets all the inclusion criteria, the research assistants will explain about the study protocol, process of data collection, and detail of TRE, behavioural economic interventions, and comparator. The patient will be asked to sign the informed consent if they are willing to participate the study.

Table 1. Study assessment schedule

Activity	Time point				
	Screening visit	**Visit 1 (baseline)**	**Visit 2 (4 week)**	**Visit 3 (8 week)**	**Visit 4 (12 week)**
Enrolment					
- Eligibility screen including assessment of age, FPG, BMI, and HbA1c	√				
- Informed consent		√			
- Allocation		√			
Intervention					
- TRE with economic behavioural intervention		√	√	√	√
- TRE		√	√	√	√
- Usual care		√	√	√	√
Assessment					

- Demographic data		√			
- Underlying diseases		√			
- Health risk behaviour		√			
- Family history of DM		√			
- Physical activity		√	√	√	√
- Sleep factors		√	√	√	√
- 24-hour food recall		√	√	√	√
- Time and risk preference		√			√
Outcomes					
- FPG		√	√	√	√
- HbA1c		√	√	√	√
- Body weight		√	√	√	√
- Blood pressure		√	√	√	√
- Fasting insulin		√	√	√	√
- Serum triglyceride		√	√	√	√
- Serum cholesterol		√	√	√	√
- LDL-cholesterol		√	√	√	√
- HDL-cholesterol		√	√	√	√
- hs-CRP		√	√	√	√

At one week after enrolment (2nd visit), participants will be interviewed by research assistants about demographic data, underlying diseases, health risk behaviours, 24-hour food recall, sleep factors, physical activity level, and time and risk preference questionnaire. Physical examination including blood pressure, body weight, and height will be measured by trained research assistants. Laboratory measurement (i.e., FPG, HbA1c, serum triglyceride, total cholesterol, LDL-C, HDL-C, fasting insulin, and hs-CRP) will be performed after fasting at least 8 hours or longer. After that participant will be randomly assigned to any of 3 groups as behavioural economic intervention plus TRE, TRE alone, and usual care.

Physical activity level, sleep factors, 24-hour food recall, body weight, SBP, DBP, and laboratory measurement will be obtained at 3rd visit (4th weeks after randomization), 4th visit (8th weeks after randomization), and 5th visit (12th weeks after randomization or the end of the study). 24-hour food recall will be collected using food diary for 7 days at each visit. INMUCAL-nutrients version 4.0 (https://inmu2.mahidol.ac.th/inmucal/index.php) will be used to calculate the dietary data to nutrient intakes. This program was developed by the Institute of Nutrition, Mahidol University, Thailand.

Data management

All data will be collected and filled in hard case record forms (CRF). All CRFs will be checked by researchers for completeness and correction before data entry. Hard CRFs will be independently computerised by two research assistants using Epidata version 3.1 software. Data will be cleaned and checked every month by investigators (US and TA). Any unclear or missing information will be cross-checked against the source documents of CRFs and medical records if required. Hospital numbers will be encrypted and kept confidentiality; unique identification number (ID) will be assigned instead to each patient. All data will be backed up using Google drive to prevent data loss.

Data monitoring

A formal data and safety monitoring board (DSMB) is not required because of no expected major adverse event from study's interventions. If adverse events are occurred, these will be managed by the trial committee, including all authors of this protocol. Recruitment and retention rates, and any protocol violations will be monitored by the trial committee via regular meeting every month.

Sample size calculation

Sample size is calculated based on a superiority trial using one way analysis of variance method in STATA version 17.0. Baseline mean and standard deviation (SD) of FPG in patients of prediabetes cohort conducted in the OFM was 105 and 9 mg/dl. We expected that receiving behavioural economic interventions plus TRE and TRE alone should be able to decrease FPG around 7% and 5% relative to the control, i.e., the FBGs were about 98 and 100 mg/dl, respectively. Type I error, power, and follow up are set at 0.05, 0.8, and 20%; a total of 114 participants with 38 per group will be required to detect these differences.

Statistical analysis

Baseline characteristics and outcomes among 3 groups will be described using mean (SD) or median (range) where appropriate for continuous data, and frequency (percentage) for categorical data. Means of primary and secondary outcomes will be compared among three groups using a mixed-effect linear regression model by regress outcome on intervention and time considering patients as a random effect (i.e., repeated measured at 4, 8, and 12 weeks) and the intervention arms (TRE with behavioural economic interventions and TRE alone versus usual care) as a fixed-effect. Marginal means and differences between any pair of the three interventions will be then estimated accordingly. Sensitivity analysis will be performed to check the robustness of the primary analyses. Independent T-test will be applied to compare means of primary and secondary outcomes at the end of the study between TRE plus behavioural economic interventions and usual care groups and to compare mean of primary

and secondary outcomes between TRE and usual care groups. Last observation carried forward (LOCF) will be applied to impute the missing outcome data for patients who are loss to follow up.

Protocol violation will be dealt using an intention to treat analysis (ITT) and per-protocol analysis (PPA). For the PPA, patients in the TRE plus behavioural economic interventions and TRE alone who do not comply with TRE (i.e., comply < 5 days per week) throughout the study or patients in the usual care group who take TRE 5 days of more per week will be excluded from analysis. Multivariate regression analysis will be applied, if there is the difference in baseline characteristics between 3 groups.

All analyses will be performed using STATA 17.0. P value less than 0.05 of 2-sided test will be considered as a statistical significance.

Patient and public involvement

None.

Ethics and dissemination

The study protocol is approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University, (MURA 2021/389) and will be conducted in agreement with the Helsinki declaration. All participants will sign informed consent at the baseline of the study (see Supplementary Appendix). Protocol amendments will be reported to the institutional ethics committee. Identification numbers will be used instead of hospital number to protect the confidentiality of study's participants. All data will be stored in database with password protection and can be accessed by only authorized staff.

Results of this study will be presented at national or international conferences and will be published in peer review journal. We plan to disseminate the results to participants, endocrinologists, and primary care physicians.

Discussion

Patients with IFG have a significant increased risk of DM. Diet interventions focused mainly on caloric restriction has been proved to decrease DM risk in this population. TRE is one type of diet intervention that has positive effects on many metabolic signal pathways from animal studies but evidence in human is limited especially in patients with IFG. Therefore, this RCT is the first study that evaluate the effect of TRE on blood sugar levels and other cardiometabolic risk factors in patients with IFG. In addition, this is the first study that assesses the impact of behavioural economic interventions such as financial incentive and text reminder on adherence to TRE intervention.

Our study design has some critical issues. First, our interventions cannot be blinded; hence, the results may be affected by observer and information bias. However, most of our outcomes are laboratory values that are objectively measured and are blinded from the outcome assessors, thus measurement error or ascertainment bias should be reduced. Second, although our study has longer term follow up than previous studies, 3-month assessment is still conserved as a short-term follow-up. Therefore, only surrogate outcomes as FPG, HbA1c, body weight, and other laboratory tests will be assessed; either a long-term effect of TRE on cardiometabolic risk factors or permanent change of participant's behaviour cannot be evaluated. Third, adherence to TRE will be measured through self-reported logbook which can be upwardly biased. However, concerning study outcomes, we consider only biological measures which will be objectively measured, e.g., FPG, HbA1c, body weight, etc. Fourth, there may be contamination of TRE in patients randomized to usual care group because TRE has been promoted in some social media in Thailand. Therefore, patients in usual care group can adopt TRE by themselves. In contrast, patients randomized to the TRE group may not comply to the TRE protocol due to intolerance to the long fasting period and will drop-out

from the study. These drawbacks may dilute the effect of TRE in our study. However, we hope that these contaminations should be minimized because we will carefully assess patients who may have already performed TRE before the beginning of this study; but once occur, this protocol violation will be dealt with ITT/PPA.

In conclusion, we will conduct a randomized controlled trial to evaluate the efficacy of behavioural economic interventions plus TRE, TRE alone, and usual care in improving FPG, HbA1c, and other cardiometabolic risk factors in patients with prediabetes. The findings from this study will be applied for the recommendation of lifestyle modification used for diabetes prevention in patients with prediabetes. Findings about the efficacy of behavioural economic intervention will inform policy makers about the novel method to help people change and maintain their healthy behaviour.

Contributors: US and TA are the principal investigators. US, TA, SB, SP, AC, SR, and AT designed the study. US and TA drafted the manuscript. US, TA, SB, SP, AC, SR, and AT critically revised the study protocol and the manuscript. The entire project will be supervised by TA, SR, and AT.

Funding: This work was supported by National Research Council of Thailand (grant number 186/2564). The funder has no role in this study.

Competing interests: None.

References

1. Aekplakorn W, Chariyalertsak S, Kessomboon P, et al. Prevalence of Diabetes and Relationship with Socioeconomic Status in the Thai Population: National Health

Examination Survey, 2004–2014. *Journal of Diabetes Research* 2018;2018:1654530. doi: 10.1155/2018/1654530

2. Porapakkham Y, Rao C, Pattaraarchachai J, et al. Estimated causes of death in Thailand, 2005: implications for health policy. *Population Health Metrics* 2010;8(1):14. doi: 10.1186/1478-7954-8-14

3. Yeboah J, Bertoni AG, Herrington DM, et al. Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2011;58(2):140-46. doi: 10.1016/j.jacc.2011.03.025

4. Toi PL, Anothaisintawee T, Chaikledkaew U, et al. Preventive Role of Diet Interventions and Dietary Factors in Type 2 Diabetes Mellitus: An Umbrella Review. *Nutrients* 2020;12(9) doi: 10.3390/nu12092722 [published Online First: 2020/09/10]

5. 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 [published Online First: 2007/04/07]

6. Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? *Obes Rev* 2011;12(7):e593-601. doi: 10.1111/j.1467-789X.2011.00873.x [published Online First: 2011/03/18]

7. Schuppelius B, Peters B, Ottawa A, et al. Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Front Endocrinol (Lausanne)* 2021;12:683140. doi: 10.3389/fendo.2021.683140 [published Online First: 2021/08/31]

8. Manoogian ENC, Zadourian A, Lo HC, et al. Protocol for a randomised controlled trial on the feasibility and effects of 10-hour time-restricted eating on cardiometabolic disease

risk among career firefighters doing 24-hour shift work: the Healthy Heroes Study. *BMJ Open* 2021;11(6):e045537. doi: 10.1136/bmjopen-2020-045537 [published Online First: 2021/06/18]

9. Anton SD, Lee SA, Donahoo WT, et al. The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* 2019;11(7) doi: 10.3390/nu11071500 [published Online First: 2019/07/03]
10. 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. doi: 10.1016/j.cmet.2019.11.004 [published Online First: 2019/12/10]
11. Schroder JD, Falqueto H, Mânica A, et al. Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021;19(1):3. doi: 10.1186/s12967-020-02687-0
12. Moon S, Kang J, Kim SH, et al. Beneficial Effects of Time-Restricted Eating on Metabolic Diseases: A Systemic Review and Meta-Analysis. *Nutrients* 2020;12(5):1267.
13. Pellegrini M, Cioffi I, Evangelista A, et al. Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Rev Endocr Metab Disord* 2020;21(1):17-33. doi: 10.1007/s11154-019-09524-w [published Online First: 2019/12/07]
14. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring)* 2019;27(5):724-32. doi: 10.1002/oby.22449 [published Online First: 2019/04/20]

15. Sutton EF, Beyl R, Early KS, et al. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metab* 2018;27(6):1212-21.e3. doi: 10.1016/j.cmet.2018.04.010 [published Online First: 2018/05/15]

16. Kesztyüs D, Cermak P, Gulich M, et al. Adherence to Time-Restricted Feeding and Impact on Abdominal Obesity in Primary Care Patients: Results of a Pilot Study in a Pre-Post Design. *Nutrients* 2019;11(12):2854. doi: 10.3390/nu11122854

17. Lee SA, Sypniewski C, Bensadon BA, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. *Nutrients* 2020;12(3):874. doi: 10.3390/nu12030874

18. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. *Jama* 2007;298(20):2415-7. doi: 10.1001/jama.298.20.2415 [published Online First: 2007/11/29]

19. Thorgeirsson T, Kawachi I. Behavioral economics: merging psychology and economics for lifestyle interventions. *Am J Prev Med* 2013;44(2):185-9. doi: 10.1016/j.amepre.2012.10.008 [published Online First: 2013/01/22]

20. Bickel WK, Moody L, Higgins ST. Some current dimensions of the behavioral economics of health-related behavior change. *Prev Med* 2016;92:16-23. doi: 10.1016/j.ypmed.2016.06.002 [published Online First: 2016/06/06]

21. Thaler RH, Sunstein CR. Nudge: Improving decisions about health, wealth, and happiness. New Haven, CT, US: Yale University Press 2008.

22. Camerer C. Behavioral economics: Reunifying psychology and economics. *Proceedings of the National Academy of Sciences* 1999;96(19):10575. doi: 10.1073/pnas.96.19.10575

23. Vlaev I, King D, Darzi A, et al. Changing health behaviors using financial incentives: a review from behavioral economics. *BMC Public Health* 2019;19(1):1059. doi: 10.1186/s12889-019-7407-8

24. Giles EL, Robalino S, McColl E, et al. The effectiveness of financial incentives for health behaviour change: systematic review and meta-analysis. *PLoS One* 2014;9(3):e90347. doi: 10.1371/journal.pone.0090347 [published Online First: 2014/03/13]

25. Volpp KG, John LK, Troxel AB, et al. Financial incentive-based approaches for weight loss: a randomized trial. *Jama* 2008;300(22):2631-7. doi: 10.1001/jama.2008.804 [published Online First: 2008/12/11]

26. Karlan D, McConnell M, Mullainathan S, et al. Getting to the Top of Mind: How Reminders Increase Saving. *Management Science* 2016;62(12):3393-411. doi: 10.1287/mnsc.2015.2296

27. Napolitano MA, Hayes S, Bennett GG, et al. Using Facebook and text messaging to deliver a weight loss program to college students. *Obesity (Silver Spring)* 2013;21(1):25-31. doi: 10.1002/oby.20232 [published Online First: 2013/03/19]

28. Patrick K, Raab F, Adams MA, et al. A text message-based intervention for weight loss: randomized controlled trial. *J Med Internet Res* 2009;11(1):e1. doi: 10.2196/jmir.1100 [published Online First: 2009/01/15]

29. Foreman KF, Stockl KM, Le LB, et al. Impact of a text messaging pilot program on patient medication adherence. *Clin Ther* 2012;34(5):1084-91. doi: 10.1016/j.clinthera.2012.04.007 [published Online First: 2012/05/05]

30. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, et al. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. *J Med Assoc Thai* 2014;97 Suppl 3:S57-67. [published Online First: 2014/04/30]

31. Pornpitakpan C. Psychometric properties of the composite scale of morningness: a shortened version. *Personality and Individual Differences* 1998;25(4):699-709. doi: https://doi.org/10.1016/S0191-8869(98)80002-0

32. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *J Phys Act Health* 2009;6(6):790-804. doi: 10.1123/jpah.6.6.790 [published Online First: 2010/01/28]

33. Cohen J, Ericson KM, Laibson D, et al. Measuring Time Preferences. *Journal of Economic Literature* 2020;58(2):299-347. doi: 10.1257/jel.20191074

34. Andersen S, Harrison GW, Lau MI, et al. Eliciting Risk and Time Preferences. *Econometrica* 2008;76(3):583-618. doi: https://doi.org/10.1111/j.1468-0262.2008.00848.x

35. Coller M, Williams MB. Eliciting Individual Discount Rates. *Experimental Economics* 1999;2(2):107-27. doi: 10.1023/A:1009986005690

36. Harrison GW, Lau MI, Williams MB. Estimating Individual Discount Rates in Denmark: A Field Experiment. *American Economic Review* 2002;92(5):1606-17. doi: 10.1257/000282802762024674

37. Andersen S, Harrison GW, Lau MI, et al. Discounting behavior: A reconsideration. *European Economic Review* 2014;71:15-33. doi: https://doi.org/10.1016/j.euroecorev.2014.06.009

38. Holt CA, Laury SK. Risk Aversion and Incentive Effects. *American Economic Review* 2002;92(5):1644-55. doi: 10.1257/000282802762024700

Patient/Participant Information Sheet

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name: Dr. Unyaporn Suthutvoravut

Research location: Ramathibodi Hospital Mahidol University

Who and how to contact when there is an emergency or disorder associated with research:
Dr. Unyaporn Suthutvoravut Tel. 0869041556
Dr. Thunyarat Anothaisintawee Tel. 0813725424

Sponsor for this research: National Research Council of Thailand

Project Background

Diabetes is a major health problem in Thailand. Diabetes is a major risk factor for cardiovascular and cerebrovascular disease. Therefore, the prevention of diabetes in the Thai population is important in reducing the mortality and disability of the Thai population in the future.
Prediabetes is a condition in which the blood sugar level is higher than normal but does not reach the diagnostic criteria for diabetes. People with pre-diabetes comparing to people with normal sugar levels are at greater risk of developing diabetes. Behavior modification through diet and exercise can reduce the risk of diabetes in people with pre-diabetes. Most dietary intervention will focus on limiting the amount of energy you get from your diet each day. Other dietary approaches other than energy restriction, such as the Intermittent time restricted eating (TRE) are now being developed to help patients make permanent behavioral changes. It is an eating style with short eating periods. and increase the duration of fasting each day to increase with or without limiting the amount of energy received from food
Previous literature shows that there have been studies on the effect of diet restriction on eating periods. It was found that diet control by having an 8-hour eating period and 16-hour fasting per day can significantly reduce body weight in people with abdominal obesity.

Objective

To study the efficacy of a time restricted-eating together with the use of behavioral economic tools to reduce blood sugar levels in people with pre-diabetes compared to time restricted-eating alone and usual care

Details to be treated with research participants

After received information about the project details, the participants sign the documents, consented to participate in this research. One week later, research assistants will conduct interviews to collect general information, history of underlying disease, risky behavior, family history of diabetes, physical activity level, diet history together with physical examination and blood test would be done to check the levels of sugar, fat and hormone. Participants will be required to fast 8-10 hours prior to the blood draw, after which they will randomly be assigned to a restricted diet, together with the use of socio-economic tool or those who received a restricted diet only for a period of time or a group that eats normally.

A time-restricted diet is a way of limiting the amount of time you eat during the day. In this study, participants will have their first meal at 8:00 AM and the last meal no later than 5:00 PM, without eating any food, snacks, fruit and beverages except water after 17: 00 until 8:00 the next day. The tool for behavioral economics is to create incentives to encourage more behavior change. The behavioral economics tool of the study was to award 1,000 baht to research participants who can maintain a restricted diet of greater than or equal to five days a week for one month in a row. Prize money will be given every month for 3 months until graduation. Participants were also given messages to encourage them to adopt a time restricted diet. The researcher will send a message every 3 days via the Line application.

After participants participated in the study at 4 weeks, 8 weeks, and 12 weeks. Blood samples will be collected. Participants will be required to fast 8-10 hours before the blood draw and interview about their eating habits. physical activity level together with physical examination by research assistant There is a compensation for the patient's time during the follow-up visit, 500 baht per time.

Benefits to the research participants

Participants will gain knowledge about diet to prevent future diabetes risk.

Side effects for the participants

There may be symptoms of low blood sugar, but the likelihood of occurrence is low Because the measures given are only recommendations for time retricted diet only, not compulsory. The patient may or may not follow the instructions. Risks associated with blood test may include pain, bleeding.

Confidentiality

The data will be collected with confidentiality. No name of number of hospital record will be collected. The data will be presented as a whole and no individual identification. Only researchers will have access to information. This study will inform patients that they are in research and able to decide whether to join or not. Patients can withdraw from research at any time and has no effect on the treatment of patients in any way.

If you have questions or concerns about participating in this research project. You can contact the chairman of the Human Research Ethics Board at Faculty Research Office, Research and Welfare Building, Faculty of Medicine Ramathibodi Hospital. Tel. 02-2011544

Informed Consent Form

Project title: Efficacy of time restricted eating and behavioral economic intervention in reducing fasting plasma glucose, HbA1c, and cardiometabolic risk factors compared to time restricted eating alone or usual care in patients with impaired fasting glucose: Protocol for a randomized controlled trial

Researcher's name, Dr. Unyaporn Suthutvoravut

Name of research participant……

Age……medical record number……

Research Participant Consent

I, Mr./Mrs./Ms…… have known the details of the research project as well as the benefits and the risks that will arise to me from the researcher clearly and consents to be involved in the above research project. And I know that if there are any problems or questions I could ask the researchers. Also, I could quit this research project at any time, without affecting the treatment that I deserve. In addition, the researchers will keep the specific information about me confidential and will only disclose it in the form of a summary of the research. Disclosure of information about me to relevant agencies could only be done in cases of necessity for academic reasons.

Signed……

(Research participant)

……..

(witness)

……..

(witness)

Date ……

Description of the doctor or researcher

I have explained the details of the project. as well as the benefits of research and the potential risks were clearly known to the participants without any hidden objection.

Signed……

(Doctor or Researcher)

date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3,8_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_____3_____
Funding	4	Sources and types of financial, material, and other support	___16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1, 16_____
	5b	Name and contact information for the trial sponsor	____16_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____16_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___16_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8-9_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____8-9____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____9_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11-13____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____-_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.