PERSONALIZING SLEEP INTERVENTIONS TO PREVENT TYPE 2 DIABETES IN COMMUNITY DWELLING ADULTS WITH PREDIABETES: A PHASE 1 SINGLE-CENTER RANDOMIZED CLINICAL TRIAL OF THE EFFECTS OF IMPROVING SLEEP ON GLYCEMIC CONTROL IN PARTICIPANTS WITH PREDIABETES

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
CGM	Continuous glucose monitoring
CSM	Composite Score of Morningness
PSQI	Pittsburgh Sleep Quality Index
T2DM	Type 2 diabetes mellitus
AHI	Apnea hypopnea index
NYULH	New York University Langone Health
CTSI	Clinical Translational Science Institute
CLIA	Clinical Laboratory Amendments
IPAQ	International Physical Activity Questionnaire

CHO	Carbohydrate
RCT	Randomized clinical trial
HbA1c	Hemoglobin A1c or glycated hemoglobin
OSA	Obstructive sleep apnea
CBT-I	Cognitive behavioral therapy for insomnia
ADA	American Diabetes Association
PHI	Protected health information
PHQ-9	Patient Health Questionnaire -9
PP	Per protocol
ITT	Intent to treat
PCP	Primary care provider
BHS	Bellevue Hospital System
CRC	Clinical Research Coordination
EMR	Electronic Medical Record
CRNP	Certified Register Nurse Practitioner
SRM-5	Social Rhythms Metric

Protocol Summary

Title	*Personalizing sleep interventions to prevent type 2 diabetes in community dwelling adults with prediabetes: A phase 1 single center randomized clinical trial of the effects of improving sleep on glycemic control in participants with prediabetes*
Short Title	*STOP T2*
Brief Summary	*A two-armed, parallel-design randomized trial of the effect of a sleep intervention on glycemic control in adults with prediabetes. The two arms will include the intervention arm (n = 94) and the attention matched control arm (n =94) for a total sample of N=188. Both arms will attend one clinic visit at baseline, a 2-week at home assessment for baseline sleep and glycemic control, 8 weekly individual intervention sessions, and a 2-week at home assessment for end of treatment sleep and glycemic control. Linear regression models will be used to assess the effect of the sleep intervention versus the control intervention on the percent time glucose is greater than or equal to 140 mg/dL.*
Phase	*Phase 1*
Objectives	*Primary objective: to determine the effect of a personalized sleep intervention on glycemic control.*
Methodology	*A single blind parallel-design randomized trial of the effect of a sleep intervention on glycemic control in adults with prediabetes.*
Endpoint	*Primary endpoint: percent time glucose is greater than or equal to 140 mg/dL*
Study Duration	*5 years*
Participant Duration	*15 weeks*
Duration of behavioral intervention	*8 weeks*
Population	*We will screen 1,000 participants in order to enroll and retain 188 adults greater than or equal to 21 years of age and less than 65 years of age diagnosed with prediabetes.*
Study Sites	*New York University*
Number of participants	*We will screen 1,000 participants in order to enroll and retain188 participants at New York University*
Description of Study Intervention/Procedure	*The sleep intervention arm will receive a personalized sleep intervention that is based on Cognitive Behavioral Therapy for Insomnia (CBT-I). Like CBT-I, the sleep intervention extends sleep based on sleep efficiency. Bedtimes and wake times will be prescribed each week for each participant and allow for gradual adjustments in sleep opportunity. Bedtimes will be set 15 minutes earlier each week provided sleep efficiency remains greater than 90%. Earlier bedtimes will extend sleep duration by increasing the opportunity for sleep. 2019 American Diabetes Association (ADA) Standards of Medical Care recommendations for physical activity and nutrition in adults with prediabetes will also be included.*
Reference Therapy	*The control arm will receive lifestyle intervention recommendations according to ADA Standard of Medical Care for physical activity and nutrition. Generic sleep recommendations will also be included.*

Key Procedures	*Baseline and end-of-treatment surveys* *Daily sleep diaries* *Weekly sleepiness surveys* *14 days of continuous wrist accelerometer wear time at baseline and end-of-treatment* *7 days of continuous glucose monitoring wear time at baseline and end-of-treatment*
Statistical Analysis	*Linear regression models will be used to assess the effect of the sleep intervention versus the control intervention on the percent time glucose is greater than or equal to 140 mg/dL. The outcome variable will be the percent time glucose is greater than or equal to 140 mg/dL. The dichotomous predictor variable will be the intervention arm (0 = control, 1 = sleep intervention).*

Schematic of Study Design

Visit 1/Day 0 CTSI visit 1 Screening

- *Total n= 800 to retain 400 for at home screening*
- *Obtain informed consent*
- *Screen potential subjects by inclusion and exclusion criteria*
- *Complete the following screening surveys (AUDIT, ARES, Insomnia Severity Index, selected questions from the Sleep Disorder Symptom Checklist (SDS-CL 25), PHQ-9, NINR Demographics)*
- *Obtain targeted health and medication history and brief physical (height, weight, waist, neck circumference, blood pressure, Hemoglobin A1c point of care test, optional blood draw)*

Weeks 1-2/Days 1 - 14 At-home screening and baseline assessments

- *Total n= 400 to retain 188 for intervention*
- *Wrist accelerometer (24/7 for 14 nights); Continuous glucose monitor (CGM) (24/7 for 7 days); Pulse oximeter (for 1 night, as needed); Sleep Diaries (daily); Social Rhythms Metrics (SRM-5), Epworth Sleepiness Scale (weekly); ASA24 hour dietary recall; Composite Scale of Morningness; International Physical Activity Questionnaire; Pittsburgh Sleep Quality Index; PROMIS-Depression 6a; Sleep Environment Survey*

Week 3/Days 15 - 21 Randomization

- *Sleep intervention group (n=94 enrolled to retain n=75)*
- *Attention control group (n=94 enrolled to retain n=75)*

Weeks 4-11/Days 22 - 77 Study Intervention

- *Administer study intervention (weekly)*
- *Sleep Diaries (daily); Epworth Sleepiness Scale (weekly)*

Visit 2/Days 78-84 CTSI visit 2.

- *ASA24 hour dietary recall; International Physical Activity Questionnaire; Pittsburgh Sleep Quality Index; PROMIS-Depression 6a*
- *Weight, waist, and blood pressure measurements*

Weeks 12-13/Days 78 - 91 End of Study Assessments

- *Wrist accelerometer to be worn 24/7 for 14 nights. Continuous glucose monitor (CGM) to be worn 24/7 for 7 days.*
- *Sleep Diaries (daily); Social Rhythms Metrics (SRM-5), Epworth Sleepiness Scale (weekly)*
- *Final visit (optional)*

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Global rates of prediabetes, a strong risk factor for T2DM, are rising[1] particularly among racial/ethnic minorities, young and middle aged adults, those living in poverty, and those with a normal BMI[2]. This trend bodes poorly for reducing T2DM incidence and its comorbidities, such as blindness and amputations[3,4]. The impact on quality of life[5-7], coupled with the economic burden for national health care budgets and for families, mandates intensified efforts to prevent and reverse prediabetes.

Prediabetes can be reversed and T2DM progression delayed through intensive lifestyle modification programs that promote weight loss by diet and exercise[8-12]. Lifestyle modification interventions are more effective in the long-term prevention of T2DM than pharmacological interventions in adults with prediabetes[13]. Disappointingly, 25 people with prediabetes need to be treated to prevent one T2DM case using lifestyle modification interventions[13]. Wide ranges in T2DM risk reduction have been reported when translating lifestyle modification programs into community settings using less intense, more affordable interventions[14-16]. Moreover, only 50% of Americans with prediabetes attempt lifestyle modifications[17]. Collectively, this evidence suggests that diet and exercise approaches are only effective for a sub-set of adults[18]. Expanding success for resistant groups and optimizing long term maintenance requires approaches beyond diet and exercise. The sleep intervention in this proposed study represents such an approach. *This proposed study is significant because it will test the effect of improving sleep on glucose in high risk groups and inform interventions for prediabetes.*

Associations between sleep duration[19-21], sleep timing[22-24], sleep regularity[25], and glycemic control in healthy adults summarized below suggest that interventions targeting these sleep dimensions will improve glycemic control. The conceptual model, adapted from Reutrakul and Knutson[26], illustrates these relationships and accounts for demographic (age, sex, race/ethnicity)[27,28], socio-economic (employment, income, education)[29-32], chronotype[28] factors, and depressive symptoms[33] that are known to influence sleep. See Figure 1.

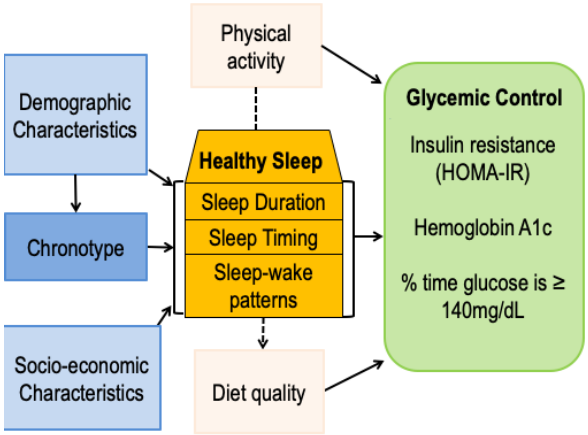

Figure 1: Conceptual model of the relationship between sleep and glycemic control

Note: Adapted from Reutrakul and Knutson (2015).

Glycemic control is influenced by sleep duration via glucose counter-regulatory hormones, appetite regulatory hormones, food reward pathway activation, diet quality, and physical activity. Hormones that counteract insulin action[34] increase during sleep restriction (e.g., growth hormone, cortisol, catecholamines)[20,21,35]. Restricting sleep alters appetite regulatory hormones[52,53], increases neuronal activation in brain regions associated with food reward[36,37], increases carbohydrate (CHO)-rich/energy-dense food intake[38-41] and is associated with reduced physical activity[42,43]. These factors contribute to weight gain and subsequent insulin resistance over time. Reduced physical activity also reduces non-insulin dependent glucose uptake by skeletal muscles[44,45]. In sum, acutely restricting sleep in healthy adults during controlled laboratory conditions worsens glycemic control by increasing insulin resistance in most[19-21,35,46], but not all[47,48], studies.

Disrupting behavioral and biological rhythms nearly doubles the effect of restricted sleep on insulin resistance[49]. Disrupted rhythms, such as altered meal and gluco-regulatory hormone alignment, stem from irregular sleep patterns and late sleep times. For example, irregular sleep patterns and late sleep times give rise to later eating opportunities that coincide with peak insulin resistance[50-52]. Eating later versus earlier meals leads to higher postprandial glucose levels[53-55], impedes weight loss efforts[56,57] and contributes to weight gain[58,59]. Weight gain and subsequent insulin resistance also stems from altered appetite regulatory hormones, increased CHO-rich/energy-dense food intake[60-63], and reduced energy expenditure (via reduced thermic response to meals)[63]. Irregular eating habits (time and frequency) that are associated with irregular sleep patterns[64] also associate with insulin resistance and postprandial

hyperglycemia[64-66]. In sum, irregular sleep patterns, caused by shifting the main sleep episode 8-12 hours, worsen glycemic control[49,50,67,68] even to prediabetic levels[67] independent of sleep duration[49] in lab studies. Some[22-24], but not all[69], studies report that habitual irregular sleep patterns of smaller magnitudes, such as 1-2 hour differences in the time of the main sleep episode between work and free days, worsens glycemic control in healthy adults. Evidence that poor glycemic control persists, even after prolonged exposure to irregular sleep patterns, is supported by the increased risk for T2DM in shift workers[70-74].

Sleep interventions studies to improve glycemic control are limited despite this collective evidence that restricted sleep and irregular sleep patterns worsen glycemic control. One lab-based crossover study reported reduced insulin resistance following 3 nights of regularizing sleep patterns and extending sleep duration compared to restricting sleep in 19 short sleeping healthy young men[75]. Another community-based study reported reduced insulin resistance following a 6-week sleep extension intervention in 16 healthy young adults[76]. Our proposed study is a randomized clinical trial (RCT) that will use wearable sensor technologies (actigraphs and continuous glucose monitors). See device table below. This will make it possible to assess temporal patterns of glycemic control across the 24-hour day in relation to sleep in adults with prediabetes, a group at greatest risk for T2DM onset and heretofore unexamined. *This proposed study is significant because it will improve sleep dimensions that are relevant to glycemic control, specifically short sleep duration and irregular sleep patterns*

Our study will complement the well-controlled lab studies linking sleep to glycemic control and determine if these findings are relevant to the everyday lives of people. Transferring lab findings to the community is hindered by the short duration of lab-based studies. Sleep, restricted to ~4-5 hours/night in the lab, is not sustainable over time in everyday life[77]. Short term lab studies prevent observing possible changes in response to prolonged conditions. This shortcoming is underscored by findings of transient insulin resistance to sleep restriction in a community based study[78]. Insulin resistance worsened during the first week of sleep restriction, corroborating laboratory evidence. However, insulin resistance declined afterwards and for the duration of the 3-week study suggesting adaptations to changes in sleep in the home environment that were not detectable in the lab. This shortcoming can have profound implications for interventions. Also, adherence to sleep interventions hinges on tailoring sleep to accommodate individual lifestyles (e.g., work demands). *This study is significant because it will identify sleep interventions most sustainable for persons in the context of their daily routines.*

Continuous glucose monitoring (CGM) and actigraphy will allow us to see how glucose fluctuates over the day in relation to sleep patterns, without disturbing sleep[79,80]. Several days of monitoring will detect delayed effects of sleep patterns on glucose[79]. Our primary outcome measure is the percent time glucose is ≥140 mg/dL (% time≥140) , one of the earliest indicators of T2DM risk[81]. High glucose variability and % time≥140 presage fasting hyperglycemia[82,83] and HbA1c elevations[84]. Postprandial hyperglycemia and glucose variability uniquely predict oxidative stress[85-87], macro and micro-vascular complications[88,89], and greater T2DM risk[90] in adults with prediabetes. CGM will estimate glucose every 5 minutes over several days and thereby detect the % time≥140 and glucose variability that may go undetected by HbA1c alone[79].

Device	Name	Manufacturer	FDA 510K clearance number	FDA approval status
Actigraph	Actiwatch Spectrum	Philips Respironics	K983533	n/a
Continuous glucose monitor	Freestyle Libre Pro	Abbott Medical	n/a	P150021
Pulse oximeter	WatchPat	Itamar	K081982	n/a

2.2 Rationale

Diet and exercise interventions have made great strides in preventing and delaying type 2 diabetes (T2DM) onset: benefits that surpass pharmacological interventions. Yet, variable responses from less intense, more affordable interventions and waning benefits over time are significant limitations. Identifying additional modifiable factors that can expand intervention options, beyond diet and exercise, are needed to sustain metabolic benefits and to reach heretofore resistant groups. One viable option is improving sleep. Multiple dimensions of sleep have been independently associated with T2DM risk and poor

glucose control in persons with T2DM. Improved insulin sensitivity has been reported in a small community based daily sleep extension study (N= 16), as well as in a 2-day lab based sleep extension study using a personalized "catch up" sleep intervention in healthy adults (N = 19,). Yet, the role of sleep in mitigating T2DM risk remains uncertain because of the small sample sizes, controlled lab conditions, and the exclusion of persons at greatest risk for T2DM in existing studies. An important but unanswered question is whether improving sleep reduces T2DM risk in high risk subgroups, such as adults with prediabetes. This study will test the effects of a sleep intervention versus a control intervention on the percentage of time glucose is ≥ 140 mg/dL in short sleeping, community-dwelling adults with pre-diabetes. Specifically, the sleep intervention aims to achieve adequate sleep duration (7-8 hours) and regular sleep patterns among enrolled participants. Wearable sensor technologies (continuous glucose monitoring and accelerometry) will be used. This study will inform personalized sleep interventions that improve glycemic responses, thus providing treatment for the prediabetic state.

2.3 Potential Risks & Benefits

2.3.1 Known Potential Risks

- *Immediate risks*

The immediate risks associated with this study are loss of confidentiality, embarrassment, local discomfort, and sleep complaints. Participants are free to refuse any procedure and to withdraw from the study at any time without repercussions. All risks will be explained to the participant.

Surveys. The main concern with the surveys relates to confidentiality and embarrassment. Loss of confidentiality will be minimized by collecting and storing all data according to standards approved by the NYULH IRB and HIPPA. Embarrassment will be minimized by allowing participants to omit any survey questions. Clinicians, sensitive to emotional responses to these surveys, will assist with administering the surveys as needed. Additionally, the survey questions used in this study have been established and used in other research studies. Participants who are psychologically distressed will be referred for appropriate treatment.

Height, waist, and weight measurements may be embarrassing or lead to a psychological reaction for participants. To minimize embarrassment or a psychological reaction, height, waist, and weights will be measured in a private area at the CTSI during visit 1. Clinicians, sensitive to emotional or physical responses to these procedures will conduct these measurements. Participants who are psychologically distressed will be referred for appropriate treatment.

Blood draws and HbA1c fingerstick for point of care testing may lead to discomfort, bruising, bleeding, or fainting. These risks will be minimized by using skilled and trained personnel to perform the fingerstick or the blood collection to minimize discomfort and potential for infection. If blood is drawn, standard procedures and analysis according to Clinical Laboratory Improvement Amendment (CLIA) standards will be followed.

Home sleep apnea monitoring may cause local discomfort while wearing the device. Participants will be given written, illustrated instructions for using the device. A 24-hour contact number to call for any problems will be provided. Participants diagnosed for the first time with moderate to severe OSA (apnea hypopnea (AHI) greater than or equal to 10) will be provided referrals to sleep clinics in the New York area for further evaluation and treatment.

Actigraphy monitoring may lead to local discomfort including skin irritation beneath the band. Wearing the accelerometer may also be inconvenient or uncomfortable. Participants will be free to remove the actigraph as needed. We will request that they note this in their sleep diary.

Inserting the *continuous glucose monitor* sensor into the back of a participant's upper arm may cause redness, pain, bruising, bleeding, or infection at the insertion site. Wearing the sensor may also be inconvenient, uncomfortable, and cause other more serious skin problems. The sensor is water-resistant and can be worn for bathing, showering or swimming. However, sensors cannot be taken in water deeper than 3 feet or for longer than 30 minutes. Sensors must be removed prior to MRI, CT scan, X-ray or diathermy treatment. Some airport full-body scanners include x-ray or millimeter radio-wave and will require the sensor to be removed if participants choose to go through these full body scanners. Also, sensors may lose adherence and fall off requiring the study team to insert another continuous glucose monitor sensor. Broken sensor probes are considered a minor risk and, although rare, are possible. To protect against a

broken sensor probe under the skin, a trained study team member will insert sensors for participants and participants will be required to verify that sensors have been removed at the end to the 7-day period.

Sleep interventions. Extending sleep may be associated with sleep complaints as well as insomnia. These risks will be protected against by personalizing sleep intervention strategies designed from the participant's habitual sleep patterns and based on an existing sleep intervention protocol. If sleep is restricted due to low sleep efficiency, participants may experience sleepiness. To protect against excessive sleepiness, participants will be monitored weekly with the Excessive Sleepiness Survey. Strategies for managing sleepiness and modifications to the sleep intervention (e.g. napping, flexible sleep schedules) will be implemented.

- *Rationale for the necessity of exposing human participants to such risks*

The rationale for the proposed research is that determining the effect of sleep on glycemic control may provide the basis for developing a T2DM lifestyle modification approach that includes sleep. This approach may improve the quality of life in adults with prediabetes and be cost effective. There is a critical need to develop personalized strategies to prevent T2DM in adults with prediabetes because they are at high risk for T2DM. Expanding success for resistant groups and optimizing long term maintenance requires approaches beyond diet and exercise. The sleep intervention in this proposed study represents such an approach.

- *Why the value of the information to be gained outweighs the risks involved*

If effective, this intervention will thwart the development of T2DM in a group at high risk for T2DM, expand treatment options to resistant groups, and optimize long term maintenance to existing lifestyle management interventions. In sum, the risks of participating in the study are outweighed by the potential benefit of thwarting the development of T2DM and improving sleep health.

- *If risk is related to proposed procedures included in protocol, any alternative procedures that have been considered and explanation on why alternative procedures not included*

The only alternative to study participation is non-participation. Non-participation will in no way affect the potential participant's medical care.

2.3.2 Known Potential Benefits

Immediate benefits for participants in the intervention arm are that participants may advance their understanding of the benefits of sleep and their metabolic risk and sleep health profile may improve. We have preliminary evidence demonstrating the effectiveness of this sleep intervention for improving sleep health (unpublished data). Others have demonstrated improvements in insulin sensitivity in normoglycemic adults following a sleep extension intervention[76]. At the end of their participation in the study, participants in the intervention and the control arms will receive a study report from the research team that will include the results from their continuous glucose monitoring and sleep assessments with an explanation of the results and recommendations for improvement.

Long range potential benefits are that participants may gain some satisfaction that their participation will advance our understanding of the relationship between sleep and T2DM risk that may someday improve preventative efforts. Improving sleep in short sleeping adults may contribute to improved health in the long run.

3 Objectives and Purpose

The overall objective of this application is to test and compare the effects of a sleep intervention versus a control condition on blood glucose in short sleeping adults with prediabetes in a randomized clinical trial. The effect on changes in blood glucose relative to baseline will be established and compared across arms. The central hypothesis is that the sleep intervention will significantly improve glycemic control compared to the control intervention.

3.1 Primary Objective

The primary objective is to determine the effect of a personalized sleep intervention on glycemic control. Our hypothesis is that the sleep intervention participants will have a lower percentage of time glucose is ≥ 140mg/dL compared to the control intervention participants after 8-weeks of treatment.

3.2 Secondary Objectives (if applicable)

The secondary objective it to determine the effect of a personalized sleep intervention on glycemic variability. Our hypothesis is that the sleep intervention participants will have a less glycemic variability compared to the control intervention participants after 8-weeks of treatment.

4 Study Design and Endpoints

4.1 Description of Study Design

This study is a phase 1, single center, single blind, parallel design randomized clinical trial. There will be two arms: 1) the sleep intervention arm and 2) the control arm. The sleep intervention arm will receive a personalized sleep intervention based on CBT-I that aims to extend sleep duration, improve sleep regularity, sleep efficiency, and sleep quality, as well as advance sleep timing. The sleep intervention arm will also receive 2019 American Diabetes Association (ADA) Standards of Medical Care recommendations for physical activity and nutrition in adults with prediabetes. The control arm will receive a time and attention matched lifestyle intervention recommendations according to ADA Standard of Medical Care for physical activity and nutrition. Generic sleep recommendations will also be included.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary outcome will be the percent time glucose is ≥ 140mg/dL, estimated from 7 days of continuous glucose monitoring. The percent time glucose is ≥ 140mg/dL was chosen as the primary endpoint because this variable is linked to postprandial glucose levels which when elevated uniquely predict oxidative stress[85-87], macro and micro-vascular complications[88,89], and greater T2DM risk[90] in adults with prediabetes. Moreover the percent time glucose is ≥ 140mg/dL, has been identified as one of the earliest indicators of T2DM risk[81] and significant differences in the percent time glucose is ≥ 140 mg/dL have been reported between people with and without prediabetes[91]. Continuous glucose monitoring results are validated measures to estimate glycemic control because continuous glucose monitoring data have been validated with blood glucose lab analyses *(r* =0.95)[92].

4.2.2 Secondary Study Endpoints

Glucose variability estimated from continuous glucose monitoring will be a secondary study endpoint because this variable has also been associated with oxidative stress[85-87], macro and micro-vascular complications[88,89].

4.2.3 Exploratory Endpoints

Exploratory endpoints will be diet quality, specifically percent carbohydrate and percent fat intake estimated from the ASA 24 diet recall, as well as physical activity estimated from the International Physical Activity Questionnaire (short form).

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. ≥ 21 years old and < 65 years old.

2. HbA1c ≥ 5.7% and < 6.5% or taking Metformin or Glucophage. Individuals with a HbA1c in this range have been identified as being at greatest risk for progressing to T2DM and for developing microvasculature complications. This will also ensure that those recruited have prediabetes.
3. ≤ 6.0 hours actigraphy-estimated sleep.
4. English speaking. Participants will need to demonstrate adequate English comprehension (assessed during informed consent). This is because the Sleep Environment Survey (used at baseline) has not been validated in other languages.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Diagnosis of T2DM or taking insulin or oral hypoglycemic medications (other than Metformin or Glucophage). The diagnosis of T2DM and treatment with anti-diabetic agents will confound continuous glucose monitoring assessments. Individuals taking metformin alone will not be excluded as metformin is frequently prescribed for prediabetes.
2. Pregnancy/lactation. Pregnancy and lactation can disrupt habitual sleep patterns and our primary interest is in recruiting individuals with habitual short sleep. Additionally, hormonal changes during pregnancy increase insulin resistance and may confound continuous glucose monitoring results[93].
3. Current chemotherapy treatments. Current chemotherapy treatments may contribute to fatigue and alter habitual sleep patterns[94].
4. Alcohol abuse/dependence may interfere with habitual sleep and limit the individual's ability to adhere to the sleep interventions. Alcohol abuse will be assessed with the Alcohol Use Disorders Identification Test (a measure that has demonstrated good reliability and validity). Individuals with scores > 15 (men) or > 13 (women) will be excluded[95].
5. Recent or planned night shift work (previous 2 months or during the intervention period) or trans-meridian travel >1 hour time zone difference during theRECR previous 4 weeks or during the intervention period. Shift work and trans-meridian travel of > 1 hour may disrupt habitual sleep and limit the individual's ability to adhere to the sleep interventions.
6. Sleep disorders (other than OSA discussed above and insomnia symptoms). Specific sleep disorders will be assessed with selected questions from the Sleep Disorders Symptom Checklist-(SDS-CL-25) that screens for narcolepsy in questions 18-20 (summed average score ≥3), restless legs syndrome in questions 15-17 (summed average score ≥3), and parasomnias in question 23 because these sleep disorders may interfere with the individual's ability to adhere to the sleep intervention.
7. Chronic use of sleep-promoting medications (self-reported) defined as taking a sleep-promoting medication ≥ 3 nights per week. Chronic use of sleep medication may interfere with sleep patterns and limit the participant's ability to take part in the sleep interventions.
8. Unstable medical illness or health condition that may interfere with habitual sleep and limit the individual's ability to adhere to the sleep interventions.
9. Unstable psychiatric illness, including the current or past diagnosis of psychotic or bipolar disorder assessed by self-report and/or medical record.
10. Moderate/severe or severe depression. Moderate-severe or severe depression will be assessed with the Patient Health Questionnaire (PHQ-9). Moderate-severe depression or severe depression may contribute to sleep disturbances and interfere with the participant's ability to adhere to the sleep interventions. Therefore, individuals with PHQ-9 scores ≥ 15 will be excluded.
11. Any condition that, in opinion of the PI, will interfere with the safe completion of the study.

5.3 Vulnerable Subjects

Children, pregnant women, fetuses, neonates, the elderly, persons with decisional incapacity, or prisoners are not included in this research study.

Employees and students may be enrolled. They will be informed that their decision to participate will not affect their academic or employment standing. No students who are under the supervisory oversight of the study team members will be enrolled.

5.4 Strategies for Recruitment and Retention

We plan to telephone screen 1,000 potential participants to enroll 800 community-dwelling, short sleeping adults (≥ 21 years and < 65) with prediabetes (defined as Hemoglobin A1c ≥ 5.7% and < 6.5%) in order to retain 188 participants who will complete the intervention. Short sleep will be defined as ≤ 6.0 hours of actigraphy-estimated sleep. Based on patients seen at New York University Langone Health (NYULH) diagnosed with prediabetes during the last year (HbA1c ≥ 5.7% and < 6.5%), we anticipate recruiting a sample consisting of 57% females, 43% males, 46% Whites, 24% Blacks, and 30% other races/ethnicities.

Prior to recruitment, IRB approval will be obtained from the New York University School of Medicine. We will recruit participants from the community by 1) electronically posting study flyers, 2) advertising in the community and via social media 3) posting flyers in clinics, 4) distributing flyers at NYULH facilities, 5) contacting past study participants who agreed to be contacted for future research studies, 6) using Epic to identify and contact potential participants, 7) using research registries such as Research Match, and 8) using a peer recruitment strategy.

All inquiries will be subjected to a structured telephone interview conducted by the project coordinator or research assistant to determine potential eligibility. If the telephone interview indicates that the potential participant may be eligible, s/he will be contacted by the project coordinator to schedule the CTSI visit 1.

1) Electronically-posted flyers: IRB-approved electronic flyers will be posted at selected sites with permission from the site. Potential sites include NYULH, Bellevue Hospital, NYU College of Dentistry, NYU College of Nursing, commuter ferries and ferry terminals, and metro terminals. Interested persons responding to the flyers will be contacted by the project coordinator or research assistant and provided with the option of proceeding with the IRB-approved telephone screening.

2) Advertising in the community: Community members may learn of the study through electronically-posted flyers or other methods, such as radio talk shows (e.g., NYU Langone Nurse Radio, sleep apnea support groups). Interested community members may contact the study team for more information about the study. After contacting the study team, the project coordinator or research assistant will provide individuals with the option of proceeding with the IRB-approved telephone screening.

3) Posted/distributed flyers: Flyers promoting the study will be available to individuals who visit the participating NYULH and Bellevue Hospital health facilities. Flyers will also be distributed at community sites so that interested individuals can contact the study team. Those responding to the distributed flyer will be contacted by the project coordinator or research assistant and provided with the option of proceeding with the IRB-approved telephone screening.

4) NYULH recruitment. This study will recruit individuals from settings affiliated with NYULH, such as employee health, occupational medicine, cardiology, endocrinology, emergency medicine, and college of nursing faculty practices. Flyers promoting this study will be available to individuals who visit the participating health facilities or attend employee health events (e.g. flu shot clinics, health fairs). Clinical staff informed of the study protocol and provided with the IRB-approved study information may also inform individuals about the study and refer them to the study team to contact if interested in participating in the study. With approval of the clinical site, the research staff will also be available at the clinical site during specific hours to facilitate recruitment. However, given the current limitations for being onsite for recruitment, this study will expand recruitment to include telephone or email recruitment of patients seeking care at all NYULH Family Health Centers and other NYULH settings. Working with the Family Health Centers and NYULH staff and scheduling personnel and NYU Langone DataCore personnel, the PI will obtain a list of patients with appointments in the NYU Langone Family Health Centers and other NYULH settings during the next month. This may include viewing the upcoming schedule in Epic. The PI will email the list of potential participants to their providers telling them their patient will be contacted about this study (the patients will be contacted via phone or email). The PI will ask the provider in this email if they have any objections to their patient's participation in the study. If there are no objections, the PI will contact the patient

telling them about the study. Patient's that do not have a primary care provider or other health care provider identified will be contacted via phone or email.

5) Past study participants. Only past study participants from the PI's and Co-I's previous studies who agreed to be contacted for future studies will be contacted by the project coordinator or research assistant. Contacted individuals expressing interest in the study will be provided with the option of proceeding with the IRB-approved telephone screening.

6) DataCore/Epic. See below.

7) Research Match. We will also utilize Research Match (ResearchMatch.org), a national, electronic, web-based recruitment tool that was created through the Clinical and Translational Science Awards Consortium in 2009 and iConnect to send study recruitment messages to potential study participants. This study's recruitment content will be inserted into the standard Research Match electronic notification that informs possible matched participants that they have been identified as a potential match for this study. The secure Research Match clearinghouse will route an IRB approved Research Match notification to each of these Research Match participants. These potentially matching participants will have the option of replying "yes", "no", or "not respond" through a set of quick links available in this notification of the study announcement. The contact information of the "yes" responding participants will be made available on the PI's "Manage my Study" dashboard. A member of the research team will contact the individual who expresses interest. If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact the study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777- 7858.

8) Peer recruitment strategy. This study will employ a hybrid sampling strategy involving targeted sampling from recruitment venues and peer recruitment. Initial seeds who are selected by study staff to recruit peers to the study, and individuals who were recruited by peers. They will be asked to recruit peers who they know by name or face, and are living with pre-diabetes. They will receive $10 for each peer who completes the CTSI screening visit.

Written informed consent will take place during the first clinic visit at the CTSI prior to any study related procedures. At the CTSI visit 1, the study details and procedures will be discussed with the project coordinator. The potential participant will be given adequate time to ask questions and review the informed consent document. Once satisfied that all questions have been answered, the potential participant will either decline to participate or sign the informed consent document. The consent form will be signed in the presence of the project coordinator. All participants must read, sign, and date a consent form before entering the study, undergoing physical examination, or undergoing any testing.

Participation retention will be enhanced by scheduling and reminding participants about weekly intervention visits, tracking the completion of daily sleep diaries, and sending email reminders if the daily sleep diary has not been completed. The study team will reach out to participants as needed to problem solve for missed sessions or missing sleep diaries.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects. A study team member will submit a request to DataCore to identify potential participants. Data points to be searched will include age, diagnosis of prediabetes, HbA1c in the prediabetic range over the previous year provided there is no diagnosis of T2DM or record of taking antidiabetic medication other than metformin (HbA1c: ≥ 5.7% and <6.5%), no diagnosis of bipolar disorder, and active MyChart participation. DataCore queries will be run at the start of the study and monthly after the study starts depending on recruitment rates. DataCore will request a report from EPIC for these patients with identifiable protected health information (name, email address) for research related purposes. Only the PI and project coordinator will have access to the search results. The Epic team will set up an IRB approved recruitment message in MyChart and work with the PI and project

coordinator to send it out. The message will include a description of the study, inclusion and exclusion criteria, and contact information for the PI (phone number and email). Participants responding that they are interested in the study will be sent a MyChart message to arrange for a convenient date and time for the telephone screen. The recruitment message may be repeated two times at one-month intervals if needed for subject recruitment (total 3 MyChart messages). These data will be used solely for participant identification in order to determine patients who are initially eligible and for chart review. If any recruitment information does need to be sent by email, the SendSafe Secure email method will be used. The study team will discard information from those who do not wish to participate in the study.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

Study participants' participation will involve a 3-4 week baseline phase that will include the CTSI visit 1, a 2 week at-home baseline assessment for sleep and glycemic control, using accelerometers (14 nights), continuous glucose monitors (7 days), and pulse oximetry (1 night, if needed). These 2 weeks will be followed by a 1-week review of the at-home data by the PI to assess continued eligibility (e.g., objectively confirmed short sleep). The at-home baseline assessment will be followed by the 8-week intervention. After the 8-week intervention, participants will return to the CTSI for the wrist accelerometer and continuous glucose monitor for the 2-week at-home end of treatment assessment. Thus, participants can anticipate involvement in the study for approximately a 15 week period.

5.6 Total Number of Participants and Sites

This is a single site study being conducted at NYULH. Recruitment will end when approximately 800 participants are enrolled. It is expected that approximately 800 participants will be enrolled in order to produce 188 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- At the discretion of the PI for lack of adherence to the intervention or study procedures or visit schedules (e.g., target 80% of weekly daily diary completion and 80% attendance at intervention sessions). Reasons for less adherence will be assessed, and if addressable will be re-evaluated at the next scheduled intervention session.
- The participant does not respond to weekly phone calls/emails for 4 weeks during the intervention.

5.7.2 Handling of Participant Withdrawals or Termination

Participants will be considered withdrawn if they cannot be contacted for 4 weeks during the intervention using all of the contact information collected. No further efforts will be made to contact the participant and that participant will be considered lost to follow-up. Abrupt termination of participation in the study intervention poses no safety risk to participants. As this study is minimal risk, efforts will not be made to collect safety and efficacy data after withdrawal. If a participant withdraws or is withdrawn from the study, no further study visits or procedures will be completed. It will be documented whether or not each subject completes the clinical study.

Any data collected before withdrawal from the study will be retained for analysis, and no new data will be collected. If the participant requests that data be destroyed, all paper records will be shredded, and any data already processed into computer files will be removed. However, if results based on the participant's data have been submitted for publication or presentation before the request is made, the results cannot be removed from the publication or presentation.

5.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, appropriate funding agency, and New York University IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

6 Behavioral/Social Intervention

6.1 Study Behavioral or Social Intervention(s) Description

Sleep Intervention Arm: The sleep intervention is based on Cognitive Behavioral Therapy for Insomnia (CBT-I). Participants may not require the initial sleep restriction that characterizes the first step of CBT-I if their sleep efficiency is > 90%. However, the sleep intervention will employ CBT-I's gradual approach for increasing sleep time and applying it to short sleepers. The 8-week intervention period of gradually increasing sleep duration by advancing bedtimes 15 minutes per week (or 1 hour per month) will provide the time needed to increase sleep duration in habitual 5 hour sleepers to the recommended 7 to 8 hour sleep duration. Like CBT-I, the sleep intervention extends sleep duration based on sleep efficiency (the proportion of time spent sleeping during a sleep episode). Bed times and wake times will be prescribed each week for each participant and allow for gradual increases in sleep opportunity. Bedtimes will be set 15 minutes earlier each week provided sleep efficiency remains >90%. Earlier betimes will extend sleep duration by increasing the opportunity for sleep. Wake times will not be changed because wake times are often determined by external demands, such as work schedules. Participants in the sleep intervention arm will receive generic nutrition, physical activity, and psycho-social self-management recommendations as per the ADA lifestyle management guidelines for adults with prediabetes.

Control Arm: The control arm will receive a time and attention matched intervention that is based on the ADA lifestyle management guidelines for adults with prediabetes. Content covered will include nutrition therapy, physical activity, and psycho-social education. Participants in the control arm will receive generic sleep hygiene recommendations.

6.1.1 Administration of Intervention

This intervention will be delivered by a trained study team member. It will consist of 8 weekly sessions. Sessions 1-8 for the intervention and control arms will consist of 45-60 minute HIPPA compliant Zoom videoconference or phone call sessions. An optional final study visit (30-minute HIPPA compliant Zoom videoconference or phone call session) will be scheduled for interested participants after all end of treatment measurements are completed and wearable technology returned (wrist accelerometer and continuous glucose monitor)

At this final visit, a study team will review the participant's baseline and end of treatment continuous glucose monitoring reports, wrist accelerometer, weight measurements, and ASA24 reports with participants.

If participants do not have access to a laptop, computer, tablet, or telephone for these sessions several alternatives will be offered to ensure that low income individuals are not excluded. A tablet will be offered to participants as needed for the duration of the intervention. Participants will return the tablets at their second CTSI visit. Alternatively, sessions may take place in-person and participants will be compensated for their travel to and from these sessions.

6.1.2 Procedures for Training Interventionalists and Monitoring Intervention Fidelity

The PI and trained study team members will be responsible for administering the intervention. We will use recommendations of the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium[98] to enhance the intervention fidelity. The treatment fidelity plan includes audiotaping each session and reviewing content against an a priori performance checklist to ensure consistency in the intervention delivery. Participants and staff will be told not to state the participant's name or any identifying information during these sessions to ensure participant confidentiality with respect to the stored audio recordings.

Treatment fidelity will be monitored by the PI and research team. Barriers to implementing the intervention will be identified and resolved.

6.1.3 Assessment of Subject Compliance with Study Intervention

The study team will track participant compliance by monitoring daily sleep diary completion, baseline and end of treatment survey completion, and weekly intervention session attendance. Retention rates for both arms will be monitored by the study team. Daily texts or email reminders will be sent to participants to remind them to complete the sleep diaries each evening as needed.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Participants meeting the telephone screen eligibility criteria will be invited to the CTSI. CTSI visit 1 will be scheduled within 4 weeks of the telephone screen. At the CTSI visit 1, participants will provide written informed consent prior to the study specific procedures listed below. All surveys at the CTSI will be completed using REDCap.

- Medical history will be obtained by completing specific surveys at the CTSI visit 1. Surveys will include: Alcohol Use Disorders Identification Test (AUDIT), ARES, Insomnia Severity Index, selected questions from the Sleep Disorder Symptom Checklist -25 , the NINR BRICS with race clarifying questions, Patient Health Questionnaire (PHQ-9), Primary care provider contact information, and a targeted health survey. Prediabetes (HbA1c $\geq$ 5.7% and < 6.5%) will be confirmed from the NYULH medical records (for NYULH participants) or from a HbA1c point of care fingerstick test (for non-NYULH participants).
- Medication history will be obtained by completing specific surveys at the CTSI visit 1. Surveys will include self-reported prescription and over-the counter medications. Specific permitted and prohibited medications will also be queried. Prohibited medications include prescribed medications for T2DM with the exception of Metformin and chronic use of prescribed or over the counter sleep medications (greater than or equal to three times per week).
- Physical examination performed at the CTSI visit will be targeted and include a measured height, waist, and weight, neck circumference, and blood pressure.

- Radiographic or other imaging assessments. Not applicable.
- Biological specimen collection and laboratory evaluations. Participants who do not have the results of a HbA1c within the previous 3 months of the CTSI visit 1 will have a Hemoglobin A1c point of care fingerstick to confirm high risk prediabetes. Participants may also be offered the option to provide a blood sample that will be de-identified for future analysis of biomarkers for metabolic disorders, sleep or circadian health, or other health conditions See Section 7.2. All blood draws will take place during the CTSI visit 1.
- A discussion of the results of any study specific procedures that will be provided to the participant include results from the 1) ARES indicating high risk for sleep apnea (≥ 6), 2) PHQ-9 indicating moderate/severe depression (>15), or 3) HbA1c test results from the CTSI visit 1 in the T2DM range (≥ 6.5%). Participants with a high-risk ARES score or previously diagnosed and currently treated OSA will complete 1 night of pulse oximetry measurements during the 2-week at home baseline assessment to confirm absence of moderate to severe OSA or the effectiveness of the current OSA treatment regime (AHI ≤ 10). Participants not previously diagnosed and treating OSA will be provided with a list of sleep clinics and encouraged to follow up with a provider for further testing and evaluation. Participants with ineffectively treated OSA will be encouraged to follow up with their health care provider managing their OSA. Participants responding “several days”, “more than half the days” or “nearly every day” to the PHQ-9 question: “Over the past 2 weeks, how often have you been bothered by any of the following problems?....Thoughts that you would be better off dead or of hurting yourself” will be screened further at the CTSI visit 1 by the project coordinator as per the Depression Safety and Referral Protocol.
- Participants with HbA1c point of care fingerstick test results from in the T2DM range of ≥ 6.5% will be provided their test results as outlined in the protocol.
- Counseling procedures. Not applicable.
- Assessment of study intervention adherence will be monitored by the completion of daily sleep diaries and by the attendance at the weekly intervention sessions.
- Administration of questionnaires or other instruments for participant outcomes, include Sleep Diaries (daily); Epworth Sleepiness Scale (weekly); and SRM-5 (daily for the 2-week baseline and 2-week end of treatment study period), ASA24 hour dietary recall (baseline and end of treatment); Composite Scale of Morningness (baseline); International Physical Activity Questionnaire (baseline and end of treatment); Pittsburgh Sleep Quality Index (baseline and end of treatment); PROMIS-Depression 6a (baseline and end of treatment); and Sleep Environment Survey (baseline) will be administered through the Assessment Center Application Programming Interface in REDCap (Research Electronic Data Capture) and during CTSI visit 2 (end of treatment surveys).
  Wearable sensor technology assessments will be as follows: pulse oximeter (baseline for 1 night, as needed); Wrist accelerometer (baseline and end of treatment 24/7 for 14 nights); Continuous glucose monitor (baseline and end of treatment 24/7 for 7 days).

7.1.2 Standard of Care Study Procedures

All participants will receive lifestyle management information for the prevention of T2DM focused on nutrition and physical activity during the intervention as per the 2019 ADA Standards of Care[99].

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Participants *without* evidence of a HbA1c within the previous 3 months or from outside the NYULH system will have a HbA1c point of care fingerstick test after enrollment (5μL). This approach is consistent with other studies examining the relationship between sleep and metabolic outcomes whereby most recent bloodwork from subject’s medical records were used[69]. Participants recruited from outside the NYULH system will have a HbA1c point of care fingerstick test after enrollment. Participants providing consent for the optional blood draw may have the blood specimen collected by peripheral vein venipuncture at the NYULH CTSI Clinical Research Center (CRC) at Bellevue Hospital C/D Building, 4th floor by the Clinical Research Coordinators. The estimated total volume of blood drawn is 20 ml.

Table 1: Blood collection			
	Volume required	Specimen type	Collection tube
Hemoglobin A1c point of care fingerstick	5μL	Whole blood	Not applicable
Optional Blood draw	20 ml	Whole blood	EDTA

7.2.2 Other Assays or Procedures

Not applicable.

7.2.3 Specimen Preparation, Handling, and Storage

All vacutainer tubes for the optional blood draw will be labeled with participants' unique study ID without PHI.

7.2.4 Specimen Shipment

Not applicable.

7.3 Study Schedule

7.3.1 Screening

Telephone Screening Visit (Day -30 to -1)

- Obtain verbal consent from potential participant to continue with the scripted telephone screen.
- Provide participants with general information about the study as per the scripted telephone screen.
- If interested, continue with the scripted telephone screen to determine potential eligibility for CTSI visit 1.
- If eligible based on telephone screen, schedule the CTSI visit 1 within 30 days of the telephone screening date.

7.3.2 Enrollment/Baseline

Enrollment/Baseline CTSI Visit 1 (Visit 1, Day 0)

- Obtain written informed consent and written audio consent of the potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Review medical history to determine eligibility based on inclusion/exclusion criteria (prediabetes diagnosis, most recent HbA1c $\geq$ 5.7% and < 6.5%, no diagnosis of current or previous bipolar disorder).
- Obtain demographic information, medical history, medication history, and alcohol use history.
- Record vital signs, results of examinations, other assessments.
- HbA1c point of care fingerstick (if needed) and blood draw for future analyses (optional).
- Provide eligible participants with instructions for the at-home assessments with wrist accelerometry, continuous glucose monitoring, pulse oximetry (if needed), and baseline surveys via REDCAp including daily sleep diaries.

7.3.3 Intermediate Visits

7.3.3.1 At-home visits

Week 1 (Days 1 - 7)

- Record adverse events as reported by participant or observed by investigator.
- Participant will wear the continuous glucose monitor for 7 days 24/7. Return the continuous glucose monitor to the study team in the prepaid package after day 14.
- If needed, participant will wear the pulse oximeter for 1 night. Return the pulse oximeter to the study team in the prepaid package after 1 night of wear time.
- Record results of continuous glucose monitor and pulse oximeter.
- Participant will wear wrist accelerometer (24/7).
- Complete Sleep Diaries (daily), SRM-5 (daily), and Epworth Sleepiness Scale (day 6)
- Complete baseline surveys: ASA24 hour dietary recall; Composite Scale of Morningness; International Physical Activity Questionnaire; Pittsburgh Sleep Quality Index; PROMIS-Depression 6a; Sleep Environment Survey.
- Record participant's adherence to intervention program.

Week 2 (Days 8 - 14)

- Record adverse events as reported by participant or observed by investigator.
- Record results of wrist accelerometer.
- Complete Sleep Diaries (daily), SRM-5 (daily) and Epworth Sleepiness Scale (day 13).
- Record participant's adherence to intervention program.

Week 3 (Days 15-21)

- Participant to ship wrist accelerometer back to the study team in the prepaid package after 14 nights of wear time (day 15).
- Record adverse events as reported by participant or observed by investigator.
- Determine eligibility for intervention based on wrist accelerometry and pulse oximetry data.
- Randomize eligible participants to sleep intervention or control arm.
- Notify participant of eligibility and arrange for weekly videoconference intervention sessions.

Weeks 4-11 (Days 22 – 77)

- Record adverse events as reported by participant or observed by investigator.
- Record results of daily Sleep Diary and weekly Epworth Sleepiness Scale results.
- Administer the study intervention to the participant in accordance with the intervention manual for the sleep intervention arm or the control arm.
- Record participant's adherence to intervention program.

7.3.4 Final Study Visits

CTSI visit 2 (Days 78-84)

- Record adverse events as reported by participant or observed by investigator.
- *Measure weight, waist, and blood pressure*
- Complete end of treatment surveys: ASA24 hour dietary recall; International Physical Activity Questionnaire; Pittsburgh Sleep Quality Index; PROMIS-Depression 6a, medical history update, and medication history update.
- Provide participants with instructions for the at-home assessments including wrist accelerometry and continuous glucose monitoring.

Week 12 (Days 78-84)

- Record adverse events as reported by participant or observed by investigator.

- Partiipant will wear the continuous glucose monitor for 7 days 24/7. Return the continuous glucose monitor to the study team in the prepaid package after day 92.
- Record results of continuous glucose monitor.
- Participant will wear wrist accelerometer (24/7).
- Complete Sleep Diaries (daily), SRM-5 (daily), and Epworth Sleepiness Scale (day 83)

Week 13 (Days 85-91)

- Record adverse events as reported by participant or observed by investigator.
- Complete Sleep Diaries (daily), SRM-5 (daily), and Epworth Sleepiness Scale (day 90)
- Participant to ship wrist accelerometer back to the study team in the prepaid package after 14 nights of wear time (day 92).
- Record results of wrist accelerometer.

Final Visit (optional)

Study team will review baseline and end of treatment continuous glucose monitoring reports, wrist accelerometer, weight measurements, and ASA24 reports with participants who are interested in this optional final visit.

7.3.5 Withdrawal Visit

If a participant withdraws or is withdrawn from the study, no further study visits or procedures will be completed.

7.3.6 Unscheduled Visit

If a participant needs an unscheduled visit for replacing the continuous glucose monitor, this visit will be arranged by the project coordinator and documented in REDCap.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Justification for Sensitive Procedures

Not applicable.

7.5.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

7.6 Prohibited Medications, Treatments, and Procedures

Not applicable.

7.7 Prophylactic Medications, Treatments, and Procedures

Not applicable.

7.8 Participant Access to Study Intervention at Study Closure

Not applicable.

8 Assessment of Safety

8.1 Specification of Safety Parameters

The study will involve no more than minimal risk to research participants. The probability and magnitude of harm or discomfort anticipated for this research are not greater than what this same population encounters in daily life or during the performance of physical or psychological examinations or tests. The only alternative to study participation is non-participation.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Intervention

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the intervention (dechallenge) should be clinically plausible.*
- ***Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
- ***Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
- ***Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
- ***Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

8.2.3 Expectedness

Dr. Susan Malone, PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the

appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

AEs are not expected due to participation in this minimal risk study. However, AE forms will be completed at each of the study assessments as well as any AEs reported during the weekly intervention sessions.

Study participants will be encouraged to contact study staff immediately should any AEs occur during study participation. Periodic adverse event reporting will include any AE that occurs while a participant is on the research protocol, regardless of whether it is considered related to study participation. The PI will submit as part of annual progress reports to the IRB a summary of monitoring that took place; cumulative adverse event data; assessments that were performed to evaluate external factors or relevant information that may have an impact on the safety of study participants or ethics of the research study; outcomes of procedural reviews conducted to ensure participant privacy and confidentiality; and final conclusions regarding changes to the anticipated risk-to-benefit ratio of study participants and recommendations related to continuing, changing, or terminating the study.

8.4.2 Serious Adverse Event Reporting

SAEs are not expected due to participation in this minimal risk study. The procedure for AE reporting will be followed for SAEs. In addition, if a serious adverse event occurs, it will be reported in a timely fashion after adjudication: All SAE reports will be made to the IRB within 5 working days; any participant deaths will be reported to the NINR Program Officer within 24 hours of realization, and all other serious adverse events will be reported to NINR within 72 hours of realization.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within the timeframe described in 8.4.2 of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within the timeframe described in 8.4.1 for AEs of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within the time frame described for AEs or SAEs, as appropriate, of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

Pregnant or breastfeeding participants will not be able participate in the study because pregnancy and lactation can disrupt habitual sleep patterns, and hormonal changes during pregnancy increase insulin resistance[93]. Female participants of child bearing potential will be asked to use a medically accepted method of birth control while in the study. If participants become pregnant during the course of the study, their data will not be used in the analyses.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Reporting Procedures – Participating Investigators

Not applicable.

8.7 Study Halting Rules

As this study is minimal risk, it is not anticipated that the study may be halted. However, if there is a determination of unexpected, significant, or unacceptable risk to participants, the study may be temporarily suspended or prematurely terminated as described in section 6.7

8.8 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Dr. Victoria Dickson, CRNP, will be the medical monitor of the study and will review participant safety data including adverse event on a monthly basis as described in this section. Dr. Dickson is a certified registered nurse practitioner (CRNP) and is qualified to oversee the safety of participants in this study. It is within the scope of practice for nurse practitioners to care for patients throughout their lifespan. This may include the diagnosis of illness and physical conditions and the performance of therapeutic and corrective measures.

Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The following are plans for data and safety monitoring during this R00 study:

Monitoring entity. This study will be monitored by the PI, the project coordinator, the bio-statistician, and the IRB. The PI will ensure that the project coordinator undergoes training in the study protocol. The project coordinator will be trained in the safety protocol for depression. The PI will oversee adherence to the study protocol to ensure the safety, reliability, and validity of data collection. The PI will be responsible for submitting all necessary reports to the study sponsor and the IRB. The project coordinator will prepare monthly reports on participant demographics, recruitment, attrition, data collection, data entry updates, and any other issues or concerns since the last research team meeting. These reports will also contain a summary of monthly accrual and cumulative accrual, a summary of key characteristics of the study participants, and a summary of the completeness and quality of data. The statistician will prepare reports about missing, invalid, or inconsistent data on selected key variables as needed.

Monitoring Study Safety. Once enrollment is initiated, the PI will arrange monthly meetings with the project coordinator and research assistant. These meetings will consist of retrospective and concurrent evaluation of all research procedures, including participant screening for inclusion/exclusion criteria, the informed consent process, and participant study instructions, as well as any necessary staff training in the IRB approved study protocol. The PI and Co-I will meet quarterly to review the study progress. Meetings will also be arranged by the PI if an adverse event occurs.

Minimizing research-associated risk. We do not believe that there are any major risks associated with the proposed study, although a subject may be identified with OSA risk, T2DM, or moderate/severe or severe depression. This is not a research-associated risks but may be detected during screening or participation in the study. The sleep intervention and accelerometry monitoring have minimal risk. Trained research personnel will perform all testing and will be monitored by the PI. Throughout the study, the PI and the research coordinator will monitor participants for adverse events and for adherence to the study protocols. We have developed the following medical alert and reporting policies:

1. ARES questionnaire $\geq$ 6
    a. For participants not eligible for the at-home assessment, refer the participant to a nearby sleep disorders center for further evaluation.
    b. For participants that are eligible for the at-home assessment, complete 1 night of at-home pulse oximetry.
2. Pulse oximetry AHI > 10
    a. Refer diagnosed and treated OSA participants to their health care provider.

b. For undiagnosed OSA participants, refer the participant to a nearby sleep disorders center for further evaluation.

3. PHQ-9 response to question 9
    a. Participants responding “several days”, “more than half the days” or “nearly every day” to the PHQ-9 question: “Over the past 2 weeks, how often have you been bothered by any of the following problems?....Thoughts that you would be better off dead or of hurting yourself” will be screened further at the CTSI visit 1 by the project coordinator as per the Depression Safety and Referral Protocol.

    b. See the Depression Safety and Referral Protocol.
4. HbA1c point of care fingerstick results ≥ 6.5%
    a. Participants will be notified of HbA1c point of care fingerstick results ≥ 6.5% at the CTSI visit.
    b. Participants will be instructed to share the results with their PCP. If the participant does not identify a PCP, the authorized prescribing provider (Dr. Dickson) is notified and a referral made to the NYU Faculty practice health care providers.

Protecting Participant Confidentiality.
Participant Screening and Enrollment. When individuals are contacted to determine their interest in participating in the study, no language will be used that will indicate any study opportunity/eligibility or personal health information unless research personnel are speaking directly with the party of interest. All data from participants screened for the study will be entered into the Research Electronic Data Capture (REDCap). The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include gender, age, race, and reason for exclusion. For retained participants, the research staff will collect and enter required data (written informed consent and demographics) onto study data forms in REDCap. Individuals will be assigned a unique study ID number.

Only the PI and the study team will have access to the linkage between the participant identity and the study identification number. This linkage will be password protected and stored on a secure NYU server.. This linking file will be destroyed at closure of the study, and the study will remain open with the IRB until these identifiers are destroyed. The unique study identification number will be used on all data forms. Paper records, such as the informed consent documents, will be kept in a locked file cabinet in a locked office. All data will be reported in aggregate.

Binders. A regulatory file will also be maintained to include the IRB- approved protocol, original informed consent documents, and other study-related regulatory documents. All paper research records and case record files will be maintained in a locked file cabinet in a secure facility within the College of Nursing. Access to the research records, study database and PHI’s will be restricted to study personnel as approved by the PI and IRB.

Data entry, processing, monitoring. This study will use REDCap for data capture and management. Data exports will be limited to the PI, the project coordinator, and the statistician for generating reports and conducting statistical data analysis. Monthly meetings will include reports on participant recruitment and retention, adverse events, and protocol deviations, as well as summaries of monthly accrual and cumulative accrual, key characteristics of the study participants, and the completeness and quality of data. Information on missing, invalid, and inconsistent data on selected key variables will be reviewed.

Data Security. All data will be saved in an electronic database on a secure NYU server. All system logins, data entries, and data updates are recorded, enabling efficient data tracking. Access to the server is available only to authorized users with passwords; overall data security is ensured by a firewall. Additional security is provided by database software requiring a password for data entry and allowing for password protection at the record level within a database. Patient confidentiality will be ensured by eliminating from the design of the data systems any information that could be used to identify individual participants. Each participant will be identified in the database by a project-specific ID number. Identifiable

information (e.g., name, birthdate, home address, or other personal information) will not be stored on any of the devices used in this study. For mobile devices and software such as the tablets or cell phones that will be used to gather survey data, guidelines established by NYU IRB will be followed including documentation of security controls, incident response program, compliance certifications, privacy practices, physical data security, and subcontractors. The packages that are shipped to and from study participants will not have any information on the exterior of the box indicating that they are a research participant.

External factors. The PI will monitor developments in the literature as the study progresses. Should it become clear that the intervention would be in any way harmful to participants, would increase risk, or would be unethical to continue, the IRB and study sponsor will be notified and the study will be stopped.

Futility analysis. As this randomized clinical trial will also be used to provide preliminary data (e.g., effect sizes) for a future well-powered R01 application, we will not do a futility analysis.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- The PI or project coordinator will audit one case per quarter, selected at random, to confirm compliance with IRB requirements, including conformance with informed consent requirements, verification of source documents, and investigator compliance.
- Authorized representatives of the IRB and the NINR may review de-identified information, as well as participants' identifiable information, for the purposes of assuring proper conduct of the research, addressing a specific reported incident, or verifying appropriate use of funds. The Quality Assurance and Quality Improvement Division of NYU's Research and Regulatory Services may audit the study to confirm compliance. Access of any protected health information will be done in the offices of the PI in his presence. No identifiable information may be copied or taken off-site.

10 Statistical Considerations

10.1 Statistical and Analytical Plans

A formal SAP will be developed for this study in consultation with the study biostatistician. Only a general overview of study statistics is included in this protocol.

10.2 Statistical Hypotheses

Sleep intervention participants will have a lower percentage of time glucose is ≥ 140mg/dL compared to control intervention participants after 8-weeks of treatment.

10.3 Analysis Datasets

Primary analyses will be performed within an intent-to-treat (ITT) sample, including all participants that are randomized to either the Sleep Intervention or Control Intervention.

10.4 Description of Statistical Methods

10.4.1 General Approach

The goal of this single site, parallel arm randomized clinical trial is to assess the impact of improved sleep on glycemic control (percent time glucose is ≥ 140) when compared to habitual sleep. Using descriptive

analyses, the investigators will describe each variable using measures of central tendency (means, medians) and variability (standard deviations, interquartile ranges) for continuous variables; counts and percentages for categorical variables. Data will be evaluated for anomalies (e.g., nonrandom missing data, erroneous outliers, multicollinearity, possible confounding) that may invalidate planned analyses. Data transformations, imputation, and/or robust and tailored analysis approaches will be used for non-normally distributed variables.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

Linear regression models will be used to assess the effect of the sleep intervention with the subject specific change in the percent time glucose is ≥ 140 from baseline as the continuous outcome variable and intervention arm (0=Control Intervention, 1=Sleep Intervention) as a dichotomous predictor. Effect sizes will be presented as beta coefficients and associated 95% confidence intervals, equal to the expected difference between the SI and CI. Important covariates that will be controlled for in these analyses include demographic characteristics including age, sex, race/ethnicity and behaviors characteristics including diet quality and physical activity. The rationale for including these covariates is because of their associations with both sleep and glycemic control. Statistical significance will be determined with a p-value < 0.05 using a two-tailed test for significance.

10.4.3 Analysis of the Secondary Endpoint(s)

The same analytic approach described in Section 10.4.2 will be used to assess the effect of the sleep intervention with the subject specific change in glucose variability.

10.4.4 Safety Analyses

As this study is minimal risk, it is not anticipated that the study may be halted. However, if there is a determination of unexpected, significant, or unacceptable risk to participants, the study may be temporarily suspended or prematurely terminated.

10.4.5 Adherence and Retention Analyses

Intervention compliance will be defined by 80% completion rate of daily sleep diaries and 80% attendance at the intervention sessions.

10.4.6 Baseline Descriptive Statistics

Demographic and other measures will be compared between the sleep intervention and control intervention arms at baseline using T-tests or Wilcoxon rank sum tests for continuous measures and chi-squared or Fisher's exact tests for categorical variables. Given the randomized nature of the study design, the two arms are expected to be balanced with respect to all baseline characteristics; in the unlikely case that there is imbalance in important covariates, these measures will be adjusted for in statistical models.

10.4.7 Planned Interim Analysis

Not applicable.

10.4.7.1 Safety Review

Not applicable.

10.4.7.2 Efficacy Review

Not applicable.

10.4.8 Additional Sub-Group Analyses

To obtain a robust estimate of the treatment effect, we will perform secondary analyses within a per-protocol (PP) sample, defined in the Sleep Intervention arm as obtaining at least 1 hour/night longer in

sleep by the end of the 8-week protocol. Controls that show over a 1 hour/night increase in their habitual sleep durations, such that they meet the above definition for investigational patients, will also be excluded from the PP sample. In our preliminary data utilizing the proposed intervention, 4 of 5 (80%) individuals met this criteria; the remaining participant almost achieved this threshold, with 57.7 minutes increased sleep; thus, we expect at least 80% of the sample to be retained in PP analyses.

Primary or secondary endpoints may be analyzed for descriptive purposes by age, race/ethnicity, or any other participant characteristic as described in detail in the SAP.

10.4.9 Multiple Comparison/Multiplicity

Not applicable.

10.4.10 Tabulation of Individual Response Data

For these analyses, the investigators will generally not control for multiple comparisons.

10.4.11 Exploratory Analyses

The same analytic approach described in Section 10.4.2 will be used to assess the effect of the sleep intervention with the subject specific change in diet quality and physical activity.

10.5 Sample Size

The primary analyses will involve comparing the mean change in the percent time glucose is ≥ 140 from baseline between the sleep intervention and control intervention arms. The study by Leproult et al[76] (N=16) reported no significant changes in insulin or glucose with sleep extension, but did not provide effect sizes for determining power; they did report large significant correlations (rho>0.6) between increased sleep time and insulin. Thus, for powering the current study, effect size assumptions come from previous research examining effects of weekend sleep extension on improvement in the calculated area under the glucose curve (Glucose AUC), which is similar to the primary endpoint we are studying here. Specifically, Killick et al[75] observed a mean improvement in Glucose AUC of 69.2 mmol min.L^{-1} (SD = 57.7) associated with weekend sleep extension; this corresponds to an effect size of ~1.2 standard deviations. If we observe this large effect, we would need 20 subjects per arm to have 95% power in the current study, at an α=0.05. To protect against over-estimates in this observed effect, which was conducted in a study with <20 individuals and relied on a different sleep intervention than proposed here, we note that 74 individuals per arm would be required to maintain 95% power in the ITT analysis set for a 50% reduction in this effect (i.e., 0.6 SDs) at an alpha of 0.05; thus, we will recruit 75 subjects per arm in the current study. Under our expectation that at least 80% will achieve our PP definition (n=60 per arm), we would maintain power of at least 90% for this effect size in the PP analysis set. To maintain power for up to 20% loss to follow-up or non-adherence during the 8-week intervention, we will plan to enroll a total of 188 participants in the two arms.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

After the 2-week at-home sleep assessment and baseline data collection, eligible participants will be randomly assigned to the sleep intervention group or to the time and attention matched control intervention group using a block randomization method. Selection bias will be reduced by using random block sizes and keeping the PI blind to the size of each block. Participants will be blinded to the group assignment. It will not be possible to blind the interventionists to the intervention. The study biostatistician will have no direct contact with study participants and will not be blinded to group assignment. The biostatistician will produce and maintain the randomization codes for the blocks. Randomization may only be unmasked by the biostatistician at the completion of analysis of the primary outcome, or for reporting of SAEs or UPs for which it will be essential to provide information to the PI on group assignment.

10.6.2 Evaluation of Success of Blinding

Blinding will be considered successful if participants remain unaware of group assignment.

10.6.3 Breaking the Study Blind/Participant Code

Participant blinding will be broken before completion of the study only for reporting of SAEs or UPs. For SAEs or UPs that could affect other participants, the entire group will be unblinded so that the PI and study staff can discuss with these participants whether it is safe for them to continue in the study.

While every effort will be made to remind interventionists not to unblind the participant, it is possible that the interventionist may unintentionally unblind the participant during the intervention. If a blind is unintentionally broken, it will be reported to the study biostatistician and discussed by the data and safety monitoring team. Any unintentional unblindings will be reported to the IRB as a deviation from protocol. The participant will be allowed to continue in the study and data will be analyzed.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol: Informed Consent (reviewed and signed at CTSI visit 1) and Audio Consent for intervention fidelity checking (reviewed and signed at CTSI visit 1).

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject, as required by the protocol.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Medical records of non-NYU patients will not be obtained. All non-NYU patients will be required to have a fingerstick for HbA1c. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the research offices of the PI at the NYU Meyers College of Nursing. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Meyers College of Nursing research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Meyers College of Nursing.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.5.1 Research Use of Stored Human Samples, Specimens, or Data

Existing or stored samples will not be used for this study.

13.6 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at the Bluestone Center for Clinical Research. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Meyers Biological Laboratory under the supervision of Dr. Susan Malone, for use by other researchers including those outside of the study. Permission to transmit data to the Meyers Biological Laboratory will be included in the informed consent. These samples could be used for research into the causes of metabolic disorders and multiple chronic conditions, its complications and other conditions for which individuals with the metabolic syndrome are at increased risk, and to improve treatment. The Meyers Biological Laboratory will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

Samples will be stored indefinitely in the Meyer's Biological Laboratory located on the 10th floor of 433 1st Avenue (Room 1068). Samples will be stored consistent with the ICF. Samples will be coded and only the NYU PI will have access to the linking key between the participant ID and the participant identity. Only researchers authorized by the PI will have access to the banked samples. Samples will be coded with freezer safe labels and stored in freezers with emergency backup power. No genetic testing will be performed in the future use of samples. Samples will be stored until they are all used up.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosamples storage will not be possible after the samples have been used.

When the study is completed, access to study data and/or samples will be provided through the Meyers Biological Laboratory.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a data capture system provided by the NYULH. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NYU IRB. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study is funded through a grant from the National Institutes of Health, National Institute of Nursing Research R00NR017416.

15.2 Costs to the Participant

Participants will not be charged for any procedures of this study.

15.3 Participant Reimbursements or Payments

This payment system reflects the significant commitment and effort that data collection is anticipated to require on the part of participants. Therefore, the guidelines for the market model of payment from Dickert and Grady will be used for the remuneration plan[100]. The function of payment in the market model is that of an incentive rather than a reward. Using this model, participants will receive a $25 gift card at enrollment, a $25 gift card after 4-weeks of the sleep intervention is complete, and a $50 when they complete the study, for a total remuneration of $100 per participant in the form of gift cards for the 15-week commitment. Transportation cost incurred by the participant for required CTSI visits will be reimbursed. $10 for recruitment of each peer who completes CTSI screening visit.

16 Study Administration

16.1 Study Leadership

The study team will govern the conduct of the study. The study team will be composed of the PI, a co-investigator, two key collaborators, a biostatistician, and a project coordinator, as listed in section 1. With the exception of NINR personnel, who will meet with the study team when required, the PI will schedule monthly study team meetings. In addition, the PI will meet individually with study team members as needed.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

1. Zhang X, Gregg EW, Williamson DF, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665-73.
2. Bullard K, Saydah S, Imperatore G, et al. Secular Changes in U.S. Prediabetes Prevalence Defined by Hemoglobin A1c and Fasting Plasma Glucose. Diabetes Care 2013;36:2286-93.
3. Menke A, Casagrande S, Geiss L, Cowie C. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. Jama 2015;314:1021-9.
4. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311-21.
5. International Diabetes Federation. IDF Diabetes Atlas. Brussels, Belgium2015.
6. Ng CS, Lee JY, Toh MP, Ko Y. Cost-of-illness studies of diabetes mellitus: a systematic review. Diabetes Res Clin Pract 2014;105:151-63.
7. Hayes A, Arima H, Woodward M, et al. Changes in Quality of Life Associated with Complications of Diabetes: Results from the ADVANCE Study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2016;19:36-41.
8. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England Journal of Medicine 2002;346:393.
9. Perreault L, Temprosa M, Mather KJ, et al. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. Diabetes Care 2014;37:2622-31.
10. Tuomilehto J, Lindstrom J, Eriksson J, et al. Prevention of Type 2 Diabetes Mellitus by changes in lifestyle among subjects with impaired glucose tolerance. New England Journal of Medicine 2001;344:1343-50.
11. Pan X, Li G, Hu Y, et al. Effects of Diet and Exercise in Preventing NIDDM in People With Impaired Glucose Tolerance: The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537-44.
12. Ramachandran A, Snehalatha C, Mary S, et al. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289-97.
13. Haw J, Galaviz K, Straus A, et al. Long-term Sustainability of Diabetes Prevention Approaches A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Internal Medicine 2017;177:1808-17.
14. Yoon U, Kwok LL, Magkidis A. Efficacy of lifestyle interventions in reducing diabetes incidence in patients with impaired glucose tolerance: a systematic review of randomized controlled trials. Metabolism 2013;62:303-14.
15. Cardona-Morrell M, Rychetnik L, Morrell S, Espinel P, Bauman A. Reduction of diabetes risk in routine clinical practice: are physical activity and nutrition interventions feasible and are the outcomes from reference trials replicable? A systematic reviewand meta-analysis. BMC public health 2010;10:653.
16. Linmans JJ, Spigt MG, Deneer L, et al. Effect of lifestyle intervention for people with diabetes or prediabetes in real-world primary care: propensity score analysis. BMC family practice 2011;12:95.
17. Geiss LS, James C, Gregg EW, Albright A, Williamson DF, Cowie CC. Diabetes risk reduction behaviors among U.S. adults with prediabetes. Am J Prev Med 2010;38:403-9.
18. Aziz Z, Absetz P, Oldroyd J, Pronk NP, Oldenburg B. A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. Implementation science : IS 2015;10:172.
19. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Annals of Internal Medicine 2012;157:549-57.
20. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.
21. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. Diabetes 2010;59:2126-33.
22. Wong PM, Hasler BP, Kamarck TW, Muldoon MF, Manuck SB. Social Jetlag, Chronotype, and Cardiometabolic Risk. J Clin Endocrinol Metab 2015;100:4612-20.
23. Parsons MJ, Moffitt TE, Gregory AM, et al. Social jetlag, obesity and metabolic disorder: investigation in a cohort study. Int J Obes (Lond) 2015;39:842-8.

24. Taylor BJ, Matthews KA, Hasler BP, et al. Bedtime Variability and Metabolic Health in Midlife Women: The SWAN Sleep Study. Sleep 2016;39:457-65.
25. Kelly RM, Finn J, Healy U, et al. Greater social jetlag associates with higher HbA1c in adults with type 2 diabetes: a cross sectional study. Sleep Med 2019;66:1-9.
26. Reutrakul S, Knutson KL. Consequences of Circadian Disruption on Cardiometabolic Health. Sleep medicine clinics 2015;10:455-68.
27. Malone SK, Patterson F, Lozano A, Hanlon A. Differences in morning-evening type and sleep duration between Black and White adults: Results from a propensity-matched UK Biobank sample. Chronobiol Int 2017;34:740-52.
28. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. Curr Biol 2012;22:939-43.
29. Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up. Ann Epidemiol 2007;17:948-55.
30. Whinnery J, Jackson N, Rattanaumpawan P, Grandner MA. Short and long sleep duration associated with race/ethnicity, sociodemographics, and socioeconomic position. Sleep 2013;37:601-11.
31. Basner M, Spaeth, A., Dinges, A. Sociodemographic characteristics and waking activities and their role in the timing and duration of sleep. Sleep 2014;37:1889-906.
32. National Sleep Foundation. Sleep in America Poll2010.
33. Plante DT, Cook JD, Goldstein MR. Objective measures of sleep duration and continuity in major depressive disorder with comorbid hypersomnolence: a primary investigation with contiguous systematic review and meta-analysis. J Sleep Res 2017.
34. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 2000;43:533-49.
35. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. J Clin Endocrinol Metab 2009;94:3242-50.
36. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. Int J Obes (Lond) 2014;38:411-6.
37. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. Nature communications 2013;4:2259.
38. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Annals of Internal Medicine 2004;141:846-50.
39. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr 2009;89:126-33.
40. St-Onge MP, Roberts AL, Chen J, et al. Short sleep duration increases energy intakes but does not change energy expenditure in normal-weight individuals. Am J Clin Nutr 2011;94:410-6.
41. Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr 2010;91:1550-9.
42. Schmid SM, Hallschmid M, Jauch-Chara K, et al. Short-term sleep loss decreases physical activity under free-living conditions but does not increase food intake under time-deprived laboratory conditions in healthy men. American Journal of Clinical Nutrition 2009;90:1476-82.
43. Booth JN, Bromley LE, Darukhanavala AP, Whitmore HR, Imperial JG, Penev PD. Reduced physical activity in adults at risk for type 2 diabetes who curtail their sleep. Obesity 2012;20:278-84.
44. Holloszy JO. Exercise-induced increase in muscle insulin sensitivity. Journal of applied physiology (Bethesda, Md : 1985) 2005;99:338-43.
45. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care 2010;33:2692-6.
46. Donga E, van Dijk M, van Dijk JG, et al. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. J Clin Endocrinol Metab 2010;95:2963-8.
47. St-Onge MP, O'Keeffe M, Roberts AL, RoyChoudhury A, Laferrere B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. Sleep 2012;35:1503-10.
48. Bosy-Westphal A, Hinrichs S, Jauch-Chara K, et al. Influence of partial sleep deprivation on energy balance and insulin sensitivity in healthy women. Obesity facts 2008;1:266-73.

49. Leproult R, Holmback U, Van Cauter E. Circadian Misalignment Augments Markers of Insulin Resistance and Inflammation, Independently of Sleep Loss. Diabetes 2014;63:1860-9.
50. Morris CJ, Yang JN, Garcia JI, et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. Proc Natl Acad Sci U S A 2015;112:E2225-34.
51. Van Cauter E, Shapiro T, Tillil H, Polonsky K. Circadian modulation of glucose and insulin responses to meals: relationship to cortisol rhythm. American journal of physiologyEndocrinology and metabolism 1992;262.
52. Boden G, Ruiz J, Urbain J, Chen X. Evidence for a circadian rhythm of insulin secretion. Am J Physiology 1996;271:E246-E52.
53. Lund J, Arendt J, Hampton S, Morgan L. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. Journal of endocrinology 2001;171:557-64.
54. Morgan L, Hampton S, Gibbs M, Arendt J. Circadian Aspects of Postprandial Metabolism. Chronobiology international 2009;20:795-808.
55. Morgan LM, Shi JW, Hampton SM, Frost G. Effect of meal timing and glycaemic index on glucose control and insulin secretion in healthy volunteers. Br J Nutr 2012;108:1286-91.
56. Garaulet M, Gomez-Abellan P, Alburquerque-Bejar JJ, Lee YC, Ordovas JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. Int J Obes (Lond) 2013;37:604-11.
57. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. Obesity 2013;21:2504-12.
58. Markwald RR, Melanson EL, Smith MR, et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. Proc Natl Acad Sci U S A 2013;110:5695-700.
59. Bandin C, Scheer FA, Luque AJ, et al. Meal timing affects glucose tolerance, substrate oxidation and circadian-related variables: A randomized, crossover trial. Int J Obes (Lond) 2015;39:828-33.
60. Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B. Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. Chronobiol Int 2009;26:544-59.
61. Lowden A, Moreno C, Holmbäck U, Lennernäs M, Tucker P. Eating and shift work – effects on habits, metabolism and performance. Scandinavian journal of work, environment & health 2010;36:150-62.
62. Cain SW, Filtness AJ, Phillips CL, Anderson C. Enhanced preference for high-fat foods following a simulated night shift. Scandinavian journal of work, environment & health 2015;41:288-93.
63. McHill AW, Melanson EL, Higgins J, et al. Impact of circadian misalignment on energy metabolism during simulated nightshift work. Proceedings of the National Academy of Sciences 2014;111:17302-7.
64. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary, insulin sensitivity, and fasting lipid profiles in healthy obese women. American Journal of Clinical Nutrition 2005;81:16-24.
65. Farshchi HR, Taylor MA, Macdonald IA. Regular meal frequency creates more appropriate insulin sensitivity and lipid profiles compared with irregular meal frequency in healthy lean women. Eur J Clin Nutr 2004;58:1071-7.
66. Mekary RA, Giovannucci E, Cahill L, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in older women: breakfast consumption and eating frequency. American Journal of Clinical Nutrition 2013;98:436-43.
67. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. Proc Natl Acad Sci U S A 2009;106:4453-8.
68. Gonnissen H, Rutters F, Mazuy C, Martens E, Adam TC, Westerterp-Plantenga M. Effect of a phase advance and phase delay of the 24-h cycle on energy metabolism, appetite, and related hormones. American Journal of Clinical Nutrition 2012:689-97.
69. Reutrakul S, Siwasaranond N, Nimitphong H, et al. Relationships among sleep timing, sleep duration and glycemic control in Type 2 diabetes in Thailand. Chronobiol Int 2015;32:1469-76.
70. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. PLoS medicine 2011;8:e1001141.
71. Morikawa Y, Nakagawa H, Miura K, et al. Shift work and the risk of diabetes mellitus among Japanese male factory workers. Scandinavian journal of work, environment & health 2005;31:179-83.

72. Suwazono Y, Sakata K, Okubo Y, et al. Long-term longitudinal study on the relationship between alternating shift work and the onset of diabetes mellitus in male Japanese workers. Journal of occupational and environmental medicine 2006;48:455-61.
73. Suwazono Y, Dochi M, Oishi M, Tanaka K, Kobayashi E, Sakata K. Shiftwork and impaired glucose metabolism: a 14-year cohort study on 7104 male workers. Chronobiol Int 2009;26:926-41.
74. Buxton OM, Cain SW, O'Connor SP, et al. Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. Science Translational Medicine 2012;4:129ra43.
75. Killick R, Hoyos CM, Melehan KL, Dungan GC, 2nd, Poh J, Liu PY. Metabolic and hormonal effects of 'catch-up' sleep in men with chronic, repetitive, lifestyle-driven sleep restriction. Clin Endocrinol (Oxf) 2015;83:498-507.
76. Leproult R, Deliens G, Gilson M, Peigneux P. Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. Sleep 2015;38:707-15.
77. Blagrove MT, Alexander C, Horne JA. The effects of chronic sleep reduction on the performance of cognitive tasks sensitive to sleep deprivation. Applicaaiton of Cogntiion Psychology 1995;9:21-40.
78. Robertson MD, Russell-Jones D, Umpleby AM, Dijk DJ. Effects of three weeks of mild sleep restriction implemented in the home environment on multiple metabolic and endocrine markers in healthy young men. Metabolism 2013;62:204-11.
79. Doherty ST, Greaves SP. Time-series analysis of continuously monitored blood glucose: the impacts of geographic and daily lifestyle factors. Journal of diabetes research 2015;2015:804341.
80. Wagner J, Tennen H, Wolpert H. Continuous glucose monitoring: A review for behavioral researchers. Psychosom Med 2012;74:356-65.
81. American Diabetes Association. Postprandial Blood Glucose. Diabetes Care 2001;24.
82. Kang X, Wang C, Lifang L, et al. Effects of Different Proportion of Carbohydrate in Breakfast on Postprandial Glucose Excursion in Normal Glucose Tolerance and Impaired Glucose Regulation Subjects. Diabetes technology & therapeutics 2013;15:569-74.
83. Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy N. Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups. Indian Journal of Endocrinology and Metabolism 2014;18:274-82.
84. Hanefeld M, Sulk S, Helbig M, Thomas A, Köhler C. Differences in Glycemic Variability Between Normoglycemic and Prediabetic Subjects. Journal of Diabetes Science and Technology 2014;8:286-90.
85. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent High Glucose Enhances Apoptosis Related to Oxidative Stress in Human Umbilical Vein Endothelial Cells The Role of Protein Kinase C and NAD(P)H-Oxidase Activation. Diabetes Care 2003;52:2795-804.
86. Monnier L, Mas E, Ginet C, et al. Activation of Oxidative Stress byAcute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes. Jama 2006;295:1681-7.
87. Piconi L, Quagliaro L, Assaloni R, et al. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. Diabetes/metabolism research and reviews 2006;22:198-203.
88. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006;91:813-9.
89. The DECODE Study Group. Glucose tolerance and cardiovascular mortality:Comparison of fasting and 2 hour diagnostic criteria. Arch Intern Med 2001;161:397-404.
90. Wang C, Lv L, Yang Y, et al. Glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus. Clin Endocrinol (Oxf) 2012;76:810-5.
91. Chakarova N, Dimova R, Grozeva G, Tankova T. Assessment of glucose variability in subjects with prediabetes. Diabetes Res Clin Pract 2019;151:56-64.
92. Nakamura K, Balo A. The Accuracy and Efficacy of the Dexcom G4 Platinum Continuous Glucose Monitoring System. J Diabetes Sci Technol 2015;9:1021-6.
93. Buchanan T, Metzger B, Freinkel N, Bergman R. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. American journal of obstetrics and gynecology 1990;162:1008-14.

94. Rha SY, Lee J. Symptom clusters during palliative chemotherapy and their influence on functioning and quality of life. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2017;25:1519-27.
95. Brooks AT, Krumlauf M, Fryer CS, et al. Critical Transitions: A Mixed Methods Examination of Sleep from Inpatient Alcohol Rehabilitation Treatment to the Community. PLoS One 2016;11:e0161725.
96. Punjabi NM. Sleep disordered breathing and cardiovascular disease: An outcome-based definition of hypopneas. American journal of respiratory and critical care medicine 2008;117:1150-5.
97. Punjabi NM, Auroora R, Patil S. Home sleep testing for obstructive sleep apnea: One night is enough! . Chest 2013;143:291-4.
98. Bellg AJ, Borrelli B, Resnick B, et al. Enhancing treatment fidelity in health behavior change studies: best practices and recommendations from the NIH Behavior Change Consortium. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 2004;23:443-51.
99. American Diabetes A. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42:S46-S60.
100. Dickert N, Grady C. WHAT'S THE PRICE OF A RESEARCH SUBJECT? APPROACHES TO PAYMENT FOR RESEARCH PARTICIPATION. New England Journal of Medicine 1999:198-203.

19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Attachment A: Schedule of Events

Attachment A

Schedule of Events

Activity	**Telephone Screen** [-30 to -1 day]	**CTSI Visit 1** [Day 0]	**Week 1** [Days 1-7]	**Week 2** [Days 8-15]	**Week 3** [Days 16-23]	**Week 4-11** [Days 24-80]	**CTSI Visit 2** [Days 81-87]	**Week 13** [Days 88-95]	**Week 14** [Days 96-103]
Study team procedures									
Telephone Screen	X								
Schedule CTSI Visit	X					X (week 8)			
Study consent		X							
Anthropometric measurements & blood pressure		X					x		
Randomization					X				
Study intervention provided						X			
Participant intervention compliance check			X	X		X		X	X
Subject Survey		X	X	X		X	X	X	X
Continuous glucose monitoring			X					X	
Wrist accelerometer			X	X				X	X
Pulse oximetry			X (1 night, if needed)						
Final visit									optional
Laboratory Assessments									
HbA1c point of care fingerstick		X (if needed)							
Optional blood draw		X							