Sleep Extension or Regularity to Reduce Diabetes Risk

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Informed Consent Process
Interested participants responding to study advertisements will call the study coordinator, who will provide a link to the prescreening questionnaire. For those who initially qualify, we will set up an appointment to meet with the person and explain the study and obtain consent. Participants recruited during routine appointments may be prescreened and consented in clinic at that time.

Written informed consent will be obtained after all details of the study have been explained by one of the study personnel and the subject has received satisfactory answers to all of his/her questions.

The PI will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. A member of the study team will obtain the written, signed informed consent of each subject, prior to performing any study-specific procedures on the subject. The study team will retain the original copy of the signed informed consent form, and a copy will be provided to the subject.

The PI will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the study team will inform subjects and obtain the informed consent of enrolled subjects for continued participation in the clinical study.

Subject Withdrawal Before Study Completion (i.e., early termination)
All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Investigators will withdraw subjects for any of the following reasons:
- Lack of compliance with the study procedures
- In the investigator's opinion, continuing in the study is not in the subject's best interest

The abrupt termination of study treatment will not affect the subject safety.

Data Collection and Follow-up on Early Withdrawal Subjects
If at any time in the study a subjects voluntary withdraws or is withdrawn by the principal investigator, he /she will not incur in any risk. There will not be any data collection or follow-up on early withdrawn subjects. There will not be an early termination visit or early end of study evaluation. In the event that patients are withdrawn from the study, additional subjects will be enrolled to achieve the overall target of subjects.

Study Protocol: Visit 1 includes consent and screening procedures. At Visit 2, participants will complete an online 24-hour dietary recall (ASA24), a CGM will be inserted, and volunteers will be provided with a wrist activity monitor (Actiwatch Spectrum Plus, Philips) with wear instructions to assess habitual sleep patterns over 1 week. During the one-week at home, they will complete hunger and appetite questionnaires (reward-based questionnaires; visual analog scales) that will be sent via REDCap links and time stamped. They will also complete 4 days of food logs. At the end of one week, they will return to the laboratory (Visit 3) and have resting metabolic rate (RMR) and bioimpedance (BIA) measured as well as another ASA24. After

completion of those assessments, participants will undergo an oral glucose tolerance test (OGTT). They will be given a new Actiwatch and a new CGM sensor will be inserted. Finally, immediately following Visit 3, participants will be randomized into one of two sleep interventions: sleep extension or sleep regularity. Sleep extension will involve extending time in bed by 2 hours. The investigator will meet with the participant to determine how best to extend bedtime given social and work obligations. This can include going to bed earlier and/or waking up later. Sleep regularity involves education about healthy sleep habits as well as instruction to implement consistent bedtimes (within 30min) over the course of the 2-week intervention. Both groups will receive text message reminders throughout the 2-week intervention regarding target bedtimes, and wake times for the extension group. During these two weeks, participants will continue to complete hunger and appetite questionnaires sent via REDCap and complete 4 days of food logs during the second week. At the end of two weeks, participants will return to the laboratory for Visit 4 to have RMR and BIA measured, undergo another OGTT, and return devices. They will also be invited to discuss their experience with the PI in a semi-structured interview. The semi-structured interview will assess acceptability by asking about satisfaction with sleep schedule intervention as well as intent to continue to try to maintain schedule. See below for more details on measurements.

Measurements

Polysomnography: An at home sleep test will be conducted to rule out obstructive sleep apnea. Participants with an AHI<15 as indicated by the home sleep test (NOX T3s, Reykjavik, Iceland) will be included in study. The NOX T3s includes a nasal cannula, RIP belts, and pulse oximetry.

Wrist Actigraphy Monitoring (WAM): Sleep duration will be assessed using waterproof wrist actigraphy monitors (Actiwatch-Spectrum, Respironics/Philips) during the entire study. Due to the unobtrusive nature of this device, habitual sleep behavior can be measured over several days. We have extensive experience working with actigraphy data, and have found a great deal of variability within individuals from day to day. Thus, at least one week of actigraphy is necessary to estimate habitual sleep patterns. Actiwatch activity monitors feature digital integration, which is the most accurate measure of both movement level and intensity. The subject completes a short sleep log each morning. We will use actigraphy to estimate total sleep duration, sleep start, and sleep end both during the habitual period and during the intervention nights. This will allow us to estimate the degree of sleep extension or regularity achieved for each subject. We will also estimate sleep fragmentation and wake after sleep onset to determine whether sleep quality has been impacted by the intervention.

Caloric Intake: We will ask participants to complete 4 days of food logs, including at least 2 work days (if employed) or 2 weekdays (if unemployed) plus at least 1 free day or weekend day, during both the baseline weekend and the second week of the intervention. We have been using food logs in ongoing studies and prior studies. Dietary analysis will be performed via these logs as well as using Meallogger software, which tracks calorie intake via photo journaling. We are not asking participants to complete more food logs due to burden and reduce quality of reporting with increasing number of days. We also ask the participant to complete Automated Self-Administered 24-hour (ASA24®) Dietary Assessment Tool during the laboratory visits to obtain additional information on food intake. The ASA24 is well validated instrument for collecting 24-hour recall data and is provided by the NIH National Cancer Institute. We are not relying solely on the ASA24, however, due to variability in eating behavior from day to day, which is why we are also using food logs. We will also be able to compare the food logs to the ASA24 data to inform our choices in a R01 application.

Questionnaires: Screening involves the Berlin, STOP-BANG, PROMIS Sleep Disturbance and Insomnia Severity Index surveys. Participants will be sent links to a REDCap survey to complete visual analog scales as well as reward-related eating (RRE) questionnaires during baseline ambulatory and the sleep interventions to be completed multiple times during those sessions. The set of four validated computerized visual analogue scales (0 to 10 cm) will assess hunger, appetite, mood, affect, and sleepiness across one day, as we have previously reported. The Power of Food Scale (PFS) provides a measure of hedonic hunger, eating for pleasure and not for physical/physiological hunger, and is not correlated with BMI. Studies have validated the PFS in identifying subjects more sensitive to the constant availability of food and its usefulness in predicting the outcome of an intervention for controlling food cravings. The Reward Based Eating Drive Scale (RED-13) assesses multiple dimensions of reward-related eating including lack of satiety, preoccupation with food, and lack of control over eating. We will pick one day in which the participant is also doing food logs and send links 4 times during the day with instructions that they should complete the survey within 30 minutes of receipt. Time when the REDCap survey was completed will be saved and we will be able to determine when the participant completed the survey. We will let the participant know during Visit 1 and remind them during Visit 2 that we will pick one day and send them links 4 times during the day and that they should complete the survey within 30 minutes of receipt, between visits 2 and 3 and again between visits 3 and 4. Time when the REDCap survey was completed will the saved and we will be able to determine when the participant completed the survey. This will also provide important feasibility information for a R01 application.

Continuous Glucose Monitoring System (CGMS): CGM provides dynamic glucose information by measuring interstitial glucose levels every 5 minutes via a subcutaneous sensor placed on the back of the upper arm. We will use the Freestyle Libre Pro System ™ (Abbott Laboratories, Alameda, CA) because (1) it does not require finger sticks or further calibration once initiated, and (2) the sensors are approved for 14 days of use. We will use CGM to measure mean 24-hour glucose levels at baseline and during the intervention. We will use established methods to measure CGM.

Indirect Calorimetry and Bioimpedance: Estimates of resting metabolic rate (RMR), carbohydrate and lipid oxidation will be obtained by indirect calorimetry using the Vmax Encore 29n respiratory gas analyzer (SensorMedics Co., Yorba Linda, CA), calibrated before each measurement using gases of known composition. Subjects will remain in bed, awake but without any activity, for the entire duration of the test. Data will be collected for a total of 45 min. Bioimpedance will also be measured to get calculations of lean and fat mass.

Assessment of insulin sensitivity and glucose tolerance via the oral glucose tolerance test (OGTT): At screening and at the end of baseline ambulatory and sleep extension sessions, a 75g fsOGTT will be performed to assess diabetes risk. At time 0, 75 g of dextrose will be administered orally, and blood samples will be collected at 0 and 120 for screening and the following times for baseline and sleep extension sessions, -10, 0, 10, 20, 30, 60, 90, 120, 150, and 180 min after glucose ingestion for the measurement of the concentration of glucose, insulin, and C-peptide at all time points. The 2-point OGTT during screening will be used to assess the presence of undiagnosed diabetes. There are several indices that can be derived from the 10-point OGTT. The Matsuda Index of whole body insulin sensitivity will be calculated.[66] Quantitative insulin-sensitivity check index (QUICKI) will be calculated from fasting insulin and glucose.[48] First phase insulin response will be estimated [67] and the Oral Disposition Index (DIo) will be calculated as the product of MI and estimated first phase of insulin.[68] Insulinogenic Index will be estimated as the ratio of the incremental insulin to glucose responses over the first 30 minutes.[69] In addition to fasting glucose, insulin, C-peptide and insulin secretion

rate (ISR) levels, the areas under the curve (AUCs) will be calculated using the trapezoid method. Homeostasis model assessment (HOMA) measures of beta cell function and insulin resistance will be calculated from fasting values. Indices of beta-cell function will be estimated from plasma glucose and C-peptide concentrations using the oral minimal model of C-peptide secretion and kinetics [70-72] and incorporating standardized parameters for C-peptide kinetics and volume of distribution.[73] Glucose levels will be measured at the bedside (Yellow Springs Instrument Company, Yellow Springs, OH). Samples will be stored for measurements of insulin, and C-peptide via standard assays.

Assays: Serum insulin and c-peptide concentrations will be measured using high-sensitivity chemiluminescence assays (Immulite, Siemens Healthineers). We have used all of these procedures in published work.

Analysis plan: Changes in mean daily glucose levels, outcomes of the OGTT, hunger/appetite and food intake (kcal/day) will be summarized using descriptive statistics. The primary analysis will compare the within-subject changes in these outcomes between baseline and the interventions using repeated measures ANOVA. We will also stratify these analyses by gender to explore whether the results vary between groups. In exploratory analyses, we will examine the association between changes in these outcomes and the amount of sleep extension or regularity using correlation analyses.

Limitations/Alternative Strategies: The controlled experimental conditions of the interventions are an important strength of the study design, but it has limitations. Recruitment and retention of participants may be challenging for a protocol involving 21 nights at home and two outpatient sessions in the laboratory. We have, however, previously been successful in completing a randomized cross-over design study that required 8 nights in the laboratory for each session. Our selection of a parallel group design for the present project is motivated by the fact that recruitment and retention in a randomized cross-over study would be more difficult. Further, we are extending time in bed or imposing bedtime regularity in the home environment, rather than conducting in-laboratory extension, to ease the burden on participants. The fact that we are only studying one racial group may also be viewed as a limitation. Examining the impact of sleep extension on appetite and metabolic disease in other racial groups would be the focus of a future project.

Expected Risks
Below are the most common risks of the procedures that will be performed in this study.

OGTT Risk
For individuals without diabetes there is no risk associated with undergoing an OGTT except for the minimal risk associated with the venipuncture.

Venipuncture Risk
The clinical procedures involve minimal discomfort associated with venipuncture. There might be slight bruising at the site, which will recover in a short period of time. There is also slight risk of inflammation of the vein or infection. The amount of blood withdrawn is minimized to prevent significant blood loss. The nurses who perform these procedures are highly trained and thus these risks are minimal. Furthermore, a study physician will be available should any medical concerns arise.

Polysomnograms (PSG) Risk

There are no risks to wearing the NOX at home sleep study test other than potential slight discomfort or irritation from the electrodes.

CGM Risk
The constant glucose monitoring (CGM) will be done by an FDA approved device (Freestyle Libre), inserted by trained study staff. The risk involves is minimal pain upon insertion. Subjects may develop irritation from adhesive. If this occurs, they can remove the sensor at any time.

Bioimpedance Testing Risk
There is a risk that the bioimpedance test would affect an implanted heart pacemaker or defibrillator, however, these subjects will not be included (per exclusion criteria). The only other risk associated with this procedure is slight discomfort when the electrodes are removed from the skin.

Actiwatch Monitor Risk
This is noninvasive monitor. It is possible that subjects may feel uncomfortable wearing the devices. Rarely, irritation can occur.

Questionnaire Risk
Some of the questions may seem personal and may make you feel uncomfortable. If you have any questions or concerns while answering these questions, please talk to a study team member.

Unknown Risks
There are no other known risks involved in any of the other measurement procedures. Participation is voluntary and participants may withdraw from the study at any time.

Protecting Against Risk
The following will be specifically instituted to protect human subjects from research risks:

- The amount of blood withdrawn will be minimized to prevent significant blood loss.
- A cooling or heating apparatus will be available in the event that local venipuncture site swelling develops.
- Risks of OGTT is only associated to the venipuncture and will be minimized by minimizing the amount of blood drawn to prevent significant blood loss. Also, the nurses who perform these procedures are highly trained and thus these risks are minimal. Furthermore, a study physician will be available should any medical concerns arise.
- All subjects, including those that discontinue participation, will receive a phone call to document any additional adverse events.
- Study records will be kept confidential. All of the information collected for this research will be stored in a locked file in the offices of the research team and will only be accessible to members of the research team working on this study. Study results will be entered into a secure computer database or RedCAP by a member of the research team. Data entered into the computer or RedCAP will not have names or birth dates, and will be identified by a unique identifier code. The keycode will be in a separate file also available only to the investigators. The database will be accessible only to members of the research team.
- There is a potential to find previously un-diagnosed diabetes or sleep disorders during this study. If a subject is found to have diabetes or a sleep disorder, we will

inform them and suggest they follow up with their primary care physician for treatment.

The study staff will take measures to minimize the risks: Before the study begins, all subjects will be provided with contact phone numbers for study staff so that subjects can contact study staff at any time during the study. When in the laboratory, subjects will be supervised continuously. Confidentiality of the subjects will be preserved, and data will be stored in locked offices.

The risks associated with blood drawing will be minimized by using sterile techniques, close supervision, and care of catheter sites, and by applying pressure to the puncture site after removal of the needle or catheter. A cooling or heating apparatus will be available in the event that local venipuncture site swelling develops. The amount of blood withdrawn will be minimized to prevent significant blood loss. A physician will be in the immediate vicinity during all invasive procedures. In the event of physical injury resulting from this research, the University of Chicago will provide free emergency medical care. During the experimental protocol, the subjects will remain under continuous supervision within the limits of the clinical research centers.

Monitoring for Safety
The study team will monitor the safety of subjects throughout the study. All adverse events and protocol deviations will be logged and tracked. Adverse events will be reviewed by the PI regularly. Any events meeting the criteria of an Unanticipated Problem (UP) will be communicated to the IRB as soon as possible upon PI knowledge.

Potential Direct benefits to subject
There may be no direct benefit to the subject for participating in this study. However, all subjects will receive the results from the laboratory tests and the results from the sleep study. Participation in this study may benefit other people in the future by helping us a better understand the effect that sleep has on metabolic health. The risks are only minimal, and the risk-to-benefit ratio is small.

Data Monitoring
Ongoing quality control procedures will be implemented for data collection, storage, and processing. The study coordinator will conduct monthly monitoring of the study database and generate a report for the PI to review. The PI will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. The frequency of data review for this study differs according to the type of data and who conducts the review, and is summarized in the table below. Standing agenda items for the monthly conference calls/meetings will include participant recruitment and retention, adverse events, protocol deviations, data integrity and overall study conduct.

Data Collection and Storage
Study data will be captured using study case report forms (CRFs) designed in REDCap. We will use the Research Electronic Data Capture (REDCap) platform, which is available at the University of Chicago to meet the proposed project needs. Data will be entered using the subject's unique study code. The key linking the subject study code to the subject identity will be kept separately.

Participants will complete surveys either on paper or directly in REDCap using a web link whenever possible. These identical questionnaires will be also available in a paper format for

those subjects who are not computer or smart phone savvy. If completed in paper format the study coordinator will enter them in REDCap.

All study data will stored on a University of Chicago, HIPAA compliant and encrypted server accessible only by the study team.

Data Sharing
We will be sharing coded data with our collaborators at Northwestern University for data analysis purpose. The shared data will not contain direct identifiers (such as name and MRN) but will contain dates, such as dates from the actigraphy data and visit dates. Additional shared data will include (but is not limited to) actigraphy data, food logs, sleep logs, and laboratory values. No raw data and individual study records will be shared outside of the University of Chicago study team.