PROTOCOL:
NCT# 01786564

IRB STU#: 00204605
Title: Home sleep and circadian phase: mediators of racial disparities in diabetes risk

PRINCIPAL INVESTIGATOR:
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OBJECTIVES:
The goal of this research project is to see if deficient sleep and/or circadian disruption are partly responsible for the increased risk of diabetes among African Americans by examining sleep in the home and measuring disease risk in the laboratory.

Specific Aim 1: Disparities in sleep and circadian timing at home

Hypothesis 1: African-Americans will have shorter habitual sleep duration (wrist actigraphy), less slow-wave sleep (polysomnography [PSG]) at home, and as our pilot data suggest, sleep at later clock times, have a later circadian phase (dim light melatonin onset [DLMO]), and thus sleep at a different circadian phase (DLMO-midpoint of sleep interval) than non-Hispanic whites.

Specific Aim 2: Association between sleep/circadian measures and diabetes risk

Hypothesis 2: Deficient sleep duration and quality (shorter habitual sleep time, less slow-wave sleep [SWS], lower slow-wave activity [SWA]), a later DLMO and sleeping at a different circadian phase (DLMO-midpoint of sleep interval) will be associated with greater diabetes risk (indicated by lower SI).

Hypothesis 3: African-Americans will have greater risk of diabetes (indicated by lower disposition index) than non-Hispanic whites and this difference will be partially and significantly mediated by differences in sleep and circadian measures (identified by Specific Aim 2).

STUDY DESIGN

INCLUSION AND EXCLUSION CRITERIA:

This study will recruit African Americans (AA) and non-Hispanic whites (WH) with equal numbers of men and women in each group completing the entire study. Ages will be 21-50 years and body mass indices (BMI) will be <40 kg/m^2. To ensure equal age and BMI distribution, we will recruit stratified by age (21-35 or 36-50 years) and BMI (<30 or 30-39 kg/m^2) within each racial group.

Each subject will undergo an overnight screening that will include a clinical examination, and routine laboratory tests (including CBC/hematocrit). An overnight PSG will be performed to rule out sleep disorders, including moderate to severe sleep-disordered breathing (apnea-hypopnea index>15/hour). We will also perform an oral glucose tolerance test (see details below). Additional inclusion criteria include no major illness and no history of psychiatric,

endocrine, cardiac or sleep disorders, and premenopausal women. Those with dyslipidemia and hypertension will be included if these conditions are controlled by a stable treatment, such as lipid-lowering or antihypertensive medications (except beta-blockers).

Exclusion criteria include: persons with diabetes, diagnosed sleep disorders, history of cardiovascular event or disease (excluding controlled hypertension), major psychiatric disorder or other major illness. Persons taking medications, including but not limited to antidepressants and hypnotics (but excluding lipid-lowering drugs and anti-hypertensive medications as mentioned above), will be excluded. Also persons regularly taking medication that affects melatonin such as beta blockers and exogenous melatonin will be excluded. We will also exclude anyone who tests positive for common drugs of abuse, people with color blindness and people who have had Lasik eye surgery, or work night shifts in the month prior to study. Participants who travel across time zones will be studied only after they have remained in the Central Time Zone (or Indiana) for one month prior to the study. Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners are also excluded.

Subjects who remain eligible after screening will then be scheduled for a one week in-home assessment, which will be followed by an 18-hour laboratory study. The subjects will be given a brief sleep diary at screening to complete prior to the naturalistic session if they are eligible for the study. This brief diary asks for bed times and wake times, which is used to set up the equipment for the at-home saliva sampling.

STUDY-WIDE NUMBER OF PARTICIPANTS:

The study was previously conducted at University of Chicago, recruitment, enrollment, and study procedures occurred from 2012 to November 2016. In that time, the study consented 176 subjects, screened 107, and had 53 subjects complete the study. Now Northwestern University will be the only site where recruitment and participation in the study will occur. See “Number of Local Participants” for total study numbers.

STUDY TIMELINES:

Each subject is expected to participate for a total of about 12 days: 1 overnight screening visit, 10 days in naturalistic session, followed by the overnight in the laboratory session. Overall duration of this protocol from signing consent form to completing of the entire study will range from 4-12 weeks. Recruitment will be completed by 5/31/2018 and primary data analysis by 5/31/2019.

STUDY ENDPOINTS:

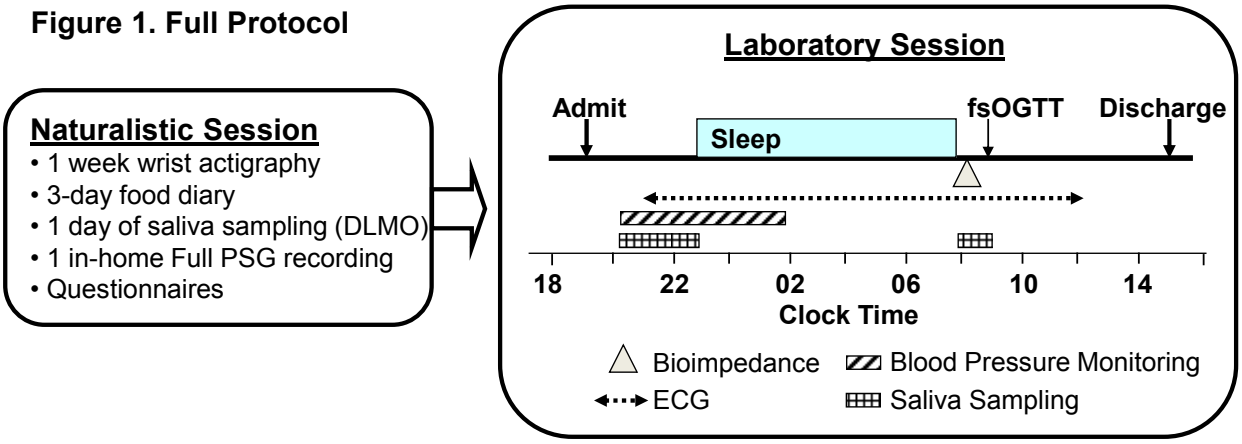
The goal of this research project is to see if deficient sleep and/or circadian disruption are partly responsible for the increased risk of diabetes among African Americans by examining sleep in the home and measuring disease risk in the laboratory.

PROCEDURES INVOLVED:

In-home assessment: The in-home assessment will last approximately 10 days during which they will continuously wear a waterproof wrist actigraphy monitor and complete sleep diaries to estimate habitual sleep duration and timing (**Figure 1**). On the Days 1 and 2 subjects will be instructed to abstain from caffeine, alcohol and NSAIDS. On Day 2 beginning in the early evening, the subjects will be instructed to collect saliva samples (details below) to estimate circadian phase (DLMO). Participants will be asked to refrain from taking NSAIDs during these two days during the in-home assessment because they suppress melatonin levels. A list of NSAIDs by both generic and commercial names will be provided along with a sample of Tylenol

to use if needed, as long as the study physician approves Tylenol use for the subject. On one of the nights after the DLMO collection (between Days 5 through 9), a mixed gender research team will visit the participant's home to pick up the saliva samples and to set up one night of unattended in-home PSG recording. A sound pressure meter and light sensor (Actiwatch-2) will be placed in the participant's bedroom the night of the PSG recording to measure sound and light levels during the sleep period. On Days 7-9, they will also complete a 3-day food diary that asks for both the amount and types of food eaten and time of meals and snacks.

Figure 1. Full Protocol



During this session, participants will also complete questionnaires that assess subjective sleep and sleepiness (Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Sleep Habits Questionnaire, Sleep Environment, Sleep Recording Experience), circadian preference (Horne-Ostberg, Munich Chronotype Questionnaire), physical activity (International Physical Activity Questionnaire – Short Version), health factors (self-rated health [1], Physical Health Questionnaire [2]., caffeine, alcohol and tobacco use) sociodemographic factors and psychosocial measures. Sociodemographic information will include employment status, education, work hours, household size, number of children, the presence of a bed partner and the MacArthur Socioeconomic Questionnaire. We will also administer several psychosocial questionnaires, including Cohen's Perceived Stress Scale [3], chronic stress questionnaire [4], three-item Loneliness Scale [5], Perceived Racism Scale [6], Interpersonal Support Evaluation List [7], the Center for Epidemiologic Studies - Depression Scale [8], and the short version of the Spielberger State-Trait Anxiety Inventory [9]. Questionnaire responses will be entered into the password-protected REDCap database and saved according to confidential study ID number.

Laboratory Session: Within one week of the in-home assessment, participants will spend approximately 21 hours in the sleep research laboratory (W4) or Clinical Research Center (W5) to obtain detailed characteristics of diabetes risk. They will be admitted to the laboratory by 17:00. Saliva samples will be collected every 30 minutes beginning 4.5 hours before bedtime, at 17:30, up to bedtime at 22:00 (total of 10 samples) for cortisol and melatonin. Time in bed in the laboratory will be from 22:00 to 8:00. PSG will be recorded if the at-home PSG is invalid. Actigraphy will be recorded through the session. Urine samples will be collected from 6:00 PM onwards until the first morning void the next morning, to test for secretion of 6-sulfatoxymelatonin (aMT6-s), a principal metabolite of melatonin excreted in urine and has been associated with glucose metabolism [10]. ELISA readouts for aMT6-s are calculated after adjusting for creatinine levels in each sample. In the morning after the first night, bioimpedance will be measured to estimate body fat percentage. Then, a 5-hour frequently-sampled oral glucose tolerance test (OGTT) will be performed. Electrocardiogram (ECG) will be measured continuously. Blood pressure (BP) will be recorded starting at 20:00 on the first day until 2:00,

which will allow for 6 hours of undisturbed sleep. Participants will be given lunch after completion of the OGTT and then discharged.

Measures of Glucose Metabolism

During the laboratory session, a 75 gm frequently-sampled oral glucose tolerance test (OGTT) will be performed. At time 0, 75 g of dextrose will be administered orally, and blood samples will be collected for the measurement of glucose, insulin, C-peptide concentrations at –10, 0, 10, 20, 30, 60, 90, 120, 150, 180, 240 and 300 min after glucose ingestion. Insulin secretion rates (ISR) will be calculated by deconvolution of C-peptide levels [11]. In addition to fasting glucose, insulin, C-peptide and 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 and the insulinogenic-index will be derived. Indexes of beta-cell function and insulin sensitivity will be estimated using the oral minimal model. Indexes 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 [12-14] and incorporating standardized parameters for C-peptide kinetics and volume of distribution [11]. Assays will be performed by validated procedures routinely used in the Endocrine Laboratory at the University of Chicago. We plan to continue to use this laboratory to maintain consistency in assay results.

During screening, an oral glucose tolerance test (OGTT) will be performed after an overnight fast to rule out the presence of diabetes. Blood samples will be taken beginning with baseline samples at -15 and 0 minutes. At time 0, 75g of glucose will be administered orally over 5 minutes. A final blood sample will then be collected at 120 minutes after ingestion. The glucose levels at 0 and 120 minutes will be used as diagnostic measures for diabetes.

Sleep Measures

Polysomnography (PSG)

Sleep will be recorded in the home, during the screening session and in the laboratory session if necessary using digital acquisition systems (Nihon Kohden, CA). Recordings will include electroencephalography (EEG), electrooculography (EOG), electromyography (EMG) and electrocardiography (ECG) signals. In addition, oronasal airflow by thermocouples and nasal pressure transducer, respiratory effort from thoracic and abdominal piezo electric belts, and pulse oximetry will be recorded at screening. Each 30-sec epoch of recording will be scored as stage Wake, I, II, III or REM following standard criteria [15,16] by an experienced rater who will be blinded to the age, gender and race of the subject. Respiratory events, periodic limb movements and microarousals will be scored according to established criteria [17,18]. Spectral analysis of EEG in the delta, theta, alpha, sigma, beta and gamma bands will be performed using the PRANA software (PhiTools, Strasbourg, France).

Wrist Actigraphy Monitoring

Sleep timing and duration will be assessed during the naturalistic and laboratory sessions using waterproof wrist actigraphy monitors (Actiwatch-2, Respironics/Philips). Due to the unobtrusive nature of this device, habitual sleep behavior can be measured over several days. Dr. Knutson has extensive experience working with actigraphy data and has found a great deal of variability within individuals from day to day [19]. Thus, a full week of actigraphy is necessary to estimate habitual sleep patterns. Participants will be asked to wear the Actiwatch continuously for the entire naturalistic session and during the laboratory session. Actiwatch activity monitors feature digital integration, which is the most accurate measure of both movement level and intensity. In order to calculate the various sleep characteristics, an estimate of bedtime and wake time is obtained from two sources, the Actiwatch event marker and the sleep log. The

Actiwatch has a button on the side that the subject presses to “mark” the data. This does not affect data collection but simply provides a mark in the data which can be used to set the bed time and wake time. The subject is also asked to complete a sleep log each morning, and this provides an additional method to determine bedtime and wake time. The combination of these two collection methods provides the most accurate determination of bedtime and wake time. Our primary measure of habitual sleep will be nocturnal sleep duration as well as the timing of sleep, however, we will also examine indicators of sleep quality (sleep efficiency, sleep fragmentation) and napping behavior.

Circadian Measures

As described above, we will collect saliva samples in the home to estimate circadian phase from the DLMO, and this will be our primary measure of circadian phase. During a start-up appointment, subjects will receive the Actiwatch, questionnaires, and at-home saliva collection kit and given ***extensive*** verbal and written instructions about the procedures. On the day of the planned saliva collection, a research assistant will call the participant at a prearranged time and remind them of the instructions for the at-home saliva collection. Collection will begin 6 hours prior to bedtime. The at-home saliva collection kit comes in a black messenger bag and consists of: a step-by-step checklist (with staff phone number), track cap bottle (with microchip in lid that records opening, MEMS, Aardex) containing 13 cotton inserts for saliva collection, 13 empty salivettes, small test tube rack, timer (PDA) with preprogrammed alarms, label dispenser (pre-labeled to avoid incorrect sample labeling), soft toothbrush (to avoid toothpaste contamination), insulated travel bag for frozen samples, 8 Tylenol pills (to avoid inadvertent use of NSAIDs), photosensor to be worn around the neck on top of clothing (Actiwatch Spectrum, wrist worn photosensors are easily covered by sleeves), and sunglasses (Noir medicals; frame style 21 or frame style 30 fitted with a filter #23) worn through the evening of the saliva sampling session until bedtime (to reduce light intensity received by the eyes while allowing for comfortable vision).

The checklist advises participants to close blinds and/or curtains to avoid outdoor light, and dim lights to a practical level (including bathroom lights). Participants are prompted by preprogrammed timer and checklist to briefly brush teeth with water 10 minutes before the first sample and before any sample if have eaten since the last sample, and at sample time open the track cap bottle, select a cotton insert, roll around in mouth for a few minutes, close track cap bottle, spit cotton insert into salivette, attach label from label dispenser and place salivette in test tube rack in freezer. At the end of the checklist, subjects remove their light medallion and go to bed. On the following night the research team that sets up the at-home PSG, will pack all frozen samples in the insulated travel bag and transport samples to the lab.

On arrival in the laboratory the saliva samples are thawed, centrifuged and then refrozen and shipped for RIA assay by SolidPhase (Portland, ME). The sensitivity of the assay is 0.7 pg/ml, intra-assay variance (<11%) and inter-assay variance (<14%). The results of the assay will be emailed to Dr. Knutson who will remove subject and condition codes and forward the data to Dr. Burgess. Dr. Burgess will calculate the DLMOs and a research assistant will confirm the scoring before the results are unblinded. As recommended by a consensus report Dr. Burgess recently coauthored [20], we will calculate the DLMO threshold as the mean of 3 low daytime points plus 2 times the SD of the 3 points. Our previous study [21] showed that in 100% of our large sample (n=170) the DLMO occurred within the 6 hour window prior to habitual bedtime. Even DLMOs of extreme night owls are captured before habitual bedtime if low thresholds for DLMO detection are used [22-24]. If we find that there are not enough low daytime points in a melatonin profile, we will follow the consensus report and use a fixed low threshold of 3 pg/ml. Very occasionally melatonin levels rise above and then fall below the threshold more than once. In this case the DLMO will be defined as when melatonin levels begin to stay above threshold for ≥ 2 h (e.g. [25]).

Dr. Burgess has a lot of experience collecting and analyzing light data and can easily identify noncompliance (e.g. artificially stable light indicates photosensor taken off). She has previously recorded ambient light levels in people's homes [25,26] and found they are naturally quite low (<50 lux). Research indicates that melatonin is not significantly suppressed by light levels this low [27] and our pilot data supports this. In addition to the DLMO we will also examine the timing of habitual sleep based on actigraphy, the timing of meals and circadian preference based on the Horne-Osberg Morningness-Eveningness questionnaire [28].

Cardiovascular and Autonomic Measurements

Systolic and diastolic arterial blood pressure will be measured at 30-minute intervals from the non-dominant arm using ambulatory monitoring equipment (Oscar II, SunTech Medical Instruments). Heart rate variability will be calculated using the ECG recording from the PSG recording. Please note Dr. Burgess is experienced in the assessment of heart rate variability measures [29-34]. We will also assay an inflammatory marker, high sensitively c-reactive protein (hsCRP), and lipids in the fasting blood samples taken during the OGTT.

Power Analysis

For the grant transfer, we calculated the sample size required to detect a difference between the whites and African Americans using the standard deviation from the already-collected data in this study for independent sample t tests. I used an alpha of .05 and a beta of .80. See Table 2 below. Sample size estimates were also calculated to detect significant associations ($p<.05$) between two continuous variables using the same standard deviations as in table below. We will have 80% power to detect a change in 1000 units of DI per 1 SD of each sleep/circadian variable with 23 subjects and we will have 80% to detect a change in 500 units of DI per 1 SD of each sleep/circadian variable with 84 subjects. Similarly, using Matsuda Index instead of DI, we can detect a change of 5 units per SD of each sleep/circadian variable (80% power, alpha=.05) with ~9 subjects and 2 units with ~40 subjects.

Table 4. Sample size required to detect differences between races.

Outcome	Mean Difference	SD	n required in each group
Sleep			
Habitual Sleep Duration	30 minutes	37.26187	25
Habitual Sleep Fragmentation	5%	4.605201	14
Slow wave sleep	30 minutes	33.62934	20
REM sleep	45 minutes	50.03308	20
DLMO-Sleep Interval	1 hour	1.183996	23
Health related			
Matsuda Index	3 units	3.734893	25
Total DI	1250 units	1609.562	27
SBP	12 mmHg	14.08113	22
DBP	7 mmHg	7.93775	7

Data Analysis

There are three main hypotheses that we plan to test. In all of these analyses our primary outcome of interest will be the Oral Disposition Index (DIo), from the OGTT, which will be tested at the $\alpha = 0.05$ level. Additional metabolic risk factors will be explored as secondary outcomes of interest, including insulin sensitivity and glucose levels. All secondary tests will be conducted

using a Bonferroni-corrected alpha level of $\alpha = 0.005$, to reduce type I errors due to multiple testing. Model assumptions will be tested with each outcome of interest and transformations of the dependent variables will be considered if the model residuals are not approximately normally distributed. All regression models described below will be checked for fit to the data through examination of residuals and other regression diagnostic techniques [35].

Linear regression models will be estimated to test for differences in the sleep and circadian measures between African Americans and whites. Covariates for which we will adjust include age, sex and BMI or body fat percentage. Secondary analysis will include examination of potential sociodemographic and psychosocial confounders of this association. Linear regression models will also be estimated to test for associations between our primary metabolic outcome, Disposition Index, and measures of sleep, including duration and percentage from actigraphy and Stage 3 and REM for PSG. Covariates for which we will adjust include age, sex, and BMI or body fat percentage, socioeconomic position and psychosocial factors.

Confidentiality

Study records will be kept confidential and data and records will be stored in locked cabinets in private offices. Electronic data files will be stored on password-protected computers. Data files and documents (with the exception of the consent form) will be stripped of identifying information and subjects will be identified only by a study ID code. Only one file will have the name and contact information linked to the study code, and this information will be linked for the duration of the study (5 years). After this time, the linked information will be destroyed.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

All adverse events, serious and non-serious, occurring during the course of the study will be collected, fully documented, and reported to the Northwestern University Internal Review Board (IRB) by the Principal Investigator, Dr. Knutson. For each adverse event, the investigator will provide the onset, duration, intensity and treatment required, outcome and action taken. We anticipate that adverse events during this study would be related to drawing blood, resulting in a bruise at the site of vein puncture, inflammation of the vein, and infection. All reasonable care will be taken to avoid these complications. In addition to adverse event reporting, the investigators will report a summary of the protocol findings, subject recruitment, drop-outs, and events to the IRB annually. The physiological studies will be conducted in the Northwestern CRU, and as such, will be overseen by the CRU Data Safety Monitoring Board. All data will be kept confidential and in a locked cabinet. Only approved study personnel will have access to study related documents.

WITHDRAWAL OF PARTICIPANTS:

Participants are free to choose to stop participation in the study at any time. They will be explicitly told that choosing not to be in this study or to stop being in this study will not result in any penalty to them or loss of benefit to which they are entitled. Specifically, the choice to withdraw will not negatively affect the right to any present or future medical treatment to which they are otherwise entitled. If participants withdraw, the procedure will immediately stop, they will be asked to fill out paperwork regarding monetary compensation for the completed portion of the study. Compensation will be prorated on the number of visits completed as described in the consent form.

The PI in charge of the study may decide to end participation at any time without participant consent. Reasons for removal may include: 1) it is in the best interest of the participants' health, 2) the participant is unable to follow the directions of the study, or 3) the participant no longer qualifies for the study, or 4) the study stops. If the PI withdraws a participant from the study, they

will always explain the reasons for doing so and will help arrange for continued care the participants own doctor, if needed.

RISKS TO PARTICIPANTS:
The clinical procedures involve minimal discomfort associated with venipuncture. There is also slight risk of inflammation of the vein or infection. However, our nurses who perform these procedures are highly trained and thus these risks are minimal. The amount of blood withdrawn is minimized to prevent significant blood loss. Baseline hematocrit will be measured in all subjects to ensure that this risk is not excessive. Furthermore, a study physician will be available should any medical concerns arise. Participation is voluntary and participants may withdraw from the study at any time.

There is potential risk of breach of privacy and confidentiality which will be minimized by having computer based data records identifiable only by a participant number. Names will not be stored with the participant data. Identifying information will be stored separately in a password protected file that will be linked to a participant number.

POTENTIAL BENEFITS TO PARTICIPANTS:
There is no direct benefit to the subject for participating in this study. The information gained from this study will help to better understand the relationship between habitual sleep behavior and characteristics in real-life conditions (i.e. the person's own home) and cardiometabolic risk. Furthermore, this study will also determine whether differences in sleep characteristics partly explain differences in diabetes risk between African Americans and whites. Ultimately, future studies may provide novel insights into the mechanisms linking impaired or insufficient sleep with the risk of cardiovascular disease, obesity and diabetes. The risks are only minimal and the risk-to-benefit ratio is very small.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
Potential risk of breach of privacy and confidentiality will be minimized by de-identifying the data with participant number. Paper copy of the surveys will be stored in a locked cabinet in the Circadian Rhythms and Sleep Research Laboratory. Each participant will be assigned a study number, and the participant name and study number will be stored in REDCap, which is only accessible to IRB-approved study team members, and requires a unique password for each user. REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online data capture for research studies. Northwestern University is a member of the REDCap consortium. All data collected from the surveys will be de-identified and entered into REDCap or an excel file that is on a password protected computer and server. Data collected from PSG and electrocardiogram will be downloaded to a password protected computer in the Circadian Rhythms and Sleep Research Laboratory for analysis. After all data is collected and analyzed, all files containing identifying information will be destroyed. Only one file will have the name and contact information linked to the study code, and this information will be linked for the duration of the study (5 years). After this time, the linked information will be destroyed.

Note this protocol involves collaboration with Dr. Helen Burgess from Rush University. Her expertise in assessing DLMO at home is required. She will assist with data analysis of melatonin to identify DLMO, but the data will all be de-identified before being shared. This protocol will also be reviewed by the IRB at Rush University.

CONSENT PROCESS:

Informed consent will be obtained by study team members or the investigator at the Northwestern University Center for Circadian and Sleep Medicine. The study procedures will be explained to interested persons and all questions will be answered. A copy of the signed consent form(s) will be given to the subject and the original document(s) will be kept in the research subject's file. Study procedures will be conducted as soon as possible after consent is obtained.

PROCESS TO DOCUMENT CONSENT IN WRITING:
An IRB approved consent form will be signed by each participant.

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Permission to Take Part in a Human Research Study

Do not sign this consent if today's date is later than the stated expiration date above.

Title of Research Study: Home sleep and circadian phase: mediators of diabetes risk

Investigator: Kristen L. Knutson, PhD Phone: (312) 503-1526

Supported By: This research is supported by the NIH, Northwestern University, and Rush University.

Key Information:

The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are a healthy adult between the ages of 21-50*.*

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this study is to determine if deficient sleep and/or disruption with the body's internal clock ("circadian rhythms") are associated with diabetes risk. This study is being done to look at the possible relationships between sleep and risk of diabetes by examining sleep in the home and diabetes risk in the laboratory.

How long will the research last and what will I need to do?

We expect that you will be in this research study for two-four weeks and require 2 overnight visits to the Hospital Clinical Research Unit.

You will participate in an overnight screening session to determine if you are eligible to participate in the study. We will conduct a sleep study with electrodes placed on your head and legs, and sensors by your nose, chest, and belly. The following morning you will also have an "oral glucose tolerance test," which measures how your body uses sugar. An IV will be inserted into your arm and blood will be sampled before and after drinking a sugary solution, totaling less than 1 teaspoon of blood. You will also have a medical examination, a urine drug screening, and a blood test.

You will then undergo the 10 day in-home assessment, which will be scheduled as soon as possible after the screening session. During this assessment you will wear a waterproof wrist activity monitor and complete various questionnaires and sleep diaries. On day 2 you will be asked to collect saliva samples every 30 minutes, starting 6 hours before your bedtime. On one of the nights between days 5 and 10, 2 members from the research team will visit your home to conduct an unattended in-home sleep recording.

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Within 1 week of the in-home assessment, you will have another overnight visit in the Hospital Clinical Research Unit. We will collect saliva samples every 30 minutes, starting 6 hours before bedtime as was done at home. Blood pressure and heart rate will be continuously recorded during this time, and urine will be collected until morning. The following morning, body fat will be measured and an oral glucose tolerance test will be performed, similar to the one conducted during the screening visit but lasting 5 hours.

More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

You may experience slight irritation at the site where polysomnography sensors are placed. You may also experience pain, irritation, or inflammation from the IV insertion and blood draws. Irritation is typically temporary and care will be taken to prevent it. There is a risk of loss of confidentiality, but all personal information will be kept in locked cabinets.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Will being in this study help me in any way?

There are no benefits to you from your taking part in this research. We hope the information learned from this study will help us further understand the relationship between sleep and diabetes.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at (312) 503-4965 or Dr. Kristen Knutson at (312) 503-1526.

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

How many people will be studied?

We expect about 200 people will consent to be in this research study.

What happens if I say "*Yes, I want to be in this research*"?

There are three parts to this study.

1. A health screening
2. An in-home assessment
3. A laboratory session

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Screening: One single overnight stay followed by approximately 4 hours in the laboratory.

In order to determine if you can participate in this study, you will go through a screening procedure. You will be asked to stay overnight in the Sleep Laboratory or Clinical Research Center in order to analyze your sleep to determine if you have any sleep disorders.

The screening will include the following:

- A sleep study with electrodes (sensors) pasted on your head to measure your brain waves and on your legs to measure your leg movements. You will also be wearing sensors that will be put in front of your nose, around your chest and belly to measure your breathing and a small sensor will be taped on your finger to measure your blood oxygen level (without collecting any blood) overnight.
- The next morning, you will have an oral glucose tolerance test (OGTT). For this test you will fast (only water and no food) beginning at 9 pm the night before the OGTT. In the morning a small flexible needle (an IV) will be inserted into a vein of your arm to allow for blood samples to be drawn. You will be given a drink (about 1 1/3 cups) which contains 75 grams of glucose (sugar). You will be asked to drink this sugar mix over 5 minutes. Twice before taking the drink and then 2 hours after drinking the sugar solution, approximately 1/3 of a teaspoon of blood will be drawn for measurement of glucose (sugar) levels. To allow for continuous blood sampling from the IV, a small amount of saline will run through the IV. In total less than 1 teaspoon of blood will be drawn during this test. This oral glucose tolerance test is designed to determine if your pancreas responds normally to this oral glucose challenge.
- You will also have a medical history, a physical examination, and urine drug screening. Also, during the OGTT, an additional 2 tablespoons of blood will be drawn for a complete blood count (CBC), liver, and kidney tests, and a urine pregnancy test for women. If you are pregnant, you will not be able to participate. If your blood count is low you may be given iron supplements and asked to come back for a repeat blood count in about 3 weeks. If the results of this test are normal you will be allowed to participate. We will also ask you to complete questionnaires of sleep, mood, energy, hunger, and appetite. The answers to some of the questions on the mood questionnaires could suggest that you have depressive symptoms. If so, you will be given the University of Chicago mental health clinic phone number for follow-up care.

In-home Assessment:

The In-home Assessment will last 10 days (see outline below) during which you will continuously wear a waterproof wrist activity monitor and complete sleep diaries to estimate sleep duration and timing. The activity monitor is a way we can get an idea of your sleep patterns by looking at the movements of your wrist. The monitor also measures the light in the room. You will also complete a 3-day food diary that asks for both the amount and types of food eaten and time of meals and snacks. On the first and second day you will be instructed to abstain from caffeine and alcohol and that afternoon and evening, and you are also asked to avoid taking any non-steroidal anti-inflammatory drugs ("NSAIDS"), including aspirin, ibuprofen (Motrin), and naproxen (Aleve, Naprosyn). We will give you a complete list of these drugs. On the second day you will be instructed to collect saliva samples every 30 minutes beginning 6 hours before your bedtime up until bedtime. We will ask you to tell us what your usual bedtime is in order to schedule this session. You will visit the laboratory either the day before Day 1 or

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on Day 1 or 2 in order to get all the equipment and the specific instructions on how to collect these samples. On one of the nights between days 5 and 10, two research team members will visit your home to pick up the saliva samples and to set up one night of unattended in-home sleep recording ("PSG"). The sleep study will include these sensors as in the screening sleep study. A sound meter and light sensor will be placed in your bedroom to measure sound and light levels during your sleep period. One of them will return in the morning to pick up this equipment. During this week, you will also complete questionnaires that ask about your sleep habits, time of day preferences for various activities, and several measures of mood and health.

Outline of In-Home Assessment

Day	Description	Note:
1	• Start wearing wrist activity monitor & complete sleep log • No alcohol, caffeine or NSAIDS	You will visit the laboratory to receive instructions and pick up the equipment either the day before day 1 or on day 1 or 2 depending on scheduling.
2	• **Saliva sampling day!** • No alcohol, caffeine or "NSAIDS" (see list) • Must be home at least one hour before first sample. (See instruction sheet) • Must wear the provided sunglasses (included in the saliva sampling package provided) • Continue to wear wrist activity monitor & complete sleep log	
3	• Start Questionnaire packet (please finish them by last day) • Continue to wear wrist activity monitor & complete sleep log	
4	• Continue to wear wrist activity monitor & complete sleep log	
5	• Continue to wear wrist activity monitor & complete sleep log	One of these nights will involve a visit by the research team to set up the sleep recording system and pick up saliva samples.
6	• Continue to wear wrist activity monitor & complete sleep log	
7	• Complete **Day 1 of Food Diary** • Continue to wear wrist activity monitor & complete sleep log	
8	• Complete **Day 2 of Food Diary** • Continue to wear wrist activity monitor & complete sleep log	
9	• Complete **Day 3 of Food Diary** • Continue to wear wrist activity monitor & complete sleep log	
10	• Complete last day of sleep log • Continue to wear wrist activity monitor • Hold on to all materials – wrist monitor, logs & questionnaires – and **bring with you to laboratory session**.	

Laboratory Session:

Within one week of the in-home assessment, you will spend approximately 21 hours in the laboratory. The day of your laboratory session, you will be instructed to abstain from caffeine and alcohol and you are also asked to avoid taking any non-steroidal anti-inflammatory drugs ("NSAIDS"), including aspirin, ibuprofen (Motrin), and naproxen (Aleve, Naprosyn). We will give you a complete list of these drugs. Please arrive at the laboratory between 5:00 PM and 5:15 PM. Saliva samples will be collected every 30 minutes between 5:25 PM and bedtime at 10:00 PM. Blood pressure will be recorded continuously between 6:00 PM and 2:00 AM. Your questionnaires will be reviewed by study personnel and a fourth food diary day will be completed. Time in bed in the laboratory will be 10:00 PM to 8:00 AM. Sleep will be recorded

using wrist activity monitoring. We may also record sleep using PSG if the home PSG did not work. Urine samples will be collected from 6:00 PM until the first morning void the next morning. In the morning, body fat will be measured. Then, an oral glucose tolerance test (OGTT) with 12 blood samples taken through an IV every 10-30 minutes over 5 hours will be performed. Total amount of blood withdrawn will be approximately 5 tablespoons. Electrocardiogram (ECG) will be measured continuously. After the OGTT you will be given lunch and then you are free to leave.

Outline of Laboratory Session

Day	Description
1	• No alcohol, caffeine or NSAIDS • Continue to wear wrist activity monitor • Arrive at lab between 5:00 & 5:15 PM • Heart rate monitoring (ECG) begins and continues throughout the session • Must wear the provided sunglasses. • Saliva samples will be collected every 30 minutes between 5:30 and 10:00PM • Blood pressure recording begins at 6:00PM and continues until 2:00AM • Sleep measured with sleep recording system and wrist activity monitoring • Urine will be collected from 6:00 PM onwards • Dinner will be provided
2	• Wake up at 8:00 AM • First morning urine will be collected • Heart rate monitoring continues • Body fat percentage measured • 5-hour Oral glucose tolerance test (involves taking blood) • Lunch at approximately 2:00 PM

During this study, Dr. Kristen Knutson and her research team will collect information about you for the purposes of this research. This information includes the following: height, weight, measure of body fat, blood pressure and heart rate recordings, and blood and urine tests for kidney and liver function, hormone response to a sugar load, and some hormone levels. We also collect sleep data, wrist activity monitoring data, and questionnaires about sleep, mood and appetite and alertness, food diaries, dates, e-mail address, names, telephone numbers, and social security number (for payment purposes).

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for completing the procedures, assessmens, and visits stated above. You are also responbile for communicating with the study coordinator or investigator when you are unable to or unwilling to continue to study.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time it will not be held against you.

If you decide to leave the research, contact the study coordinator or investigator so that they can cancel scheduled visits and assess the payment you qualify for according to the breakdown detailed later in this document.

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Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment, your class standing (for students enrolled in a class at NU), or your present or future employment (for employees at NU or its affiliates).

Detailed Risks: Is there any way being in this study could be bad for me?

This research may hurt you in the following ways:

- There is a slight risk of irritation at the site of the electrode (sensor) placement for polysomnography. This irritation would be temporary and care will be taken to avoid any irritation.
- There is the risk of loss of confidentiality of your information. All data will be kept in locked cabinets in research offices and care will be taken to prevent loss of confidentiality.
- Temporary pain, slight bruising, possible inflammation, and possible fainting may occur from IV insertion during the oral glucose tolerance tests.
- Low blood glucose levels during the oral glucose tolerance test may also result in lightheadedness, rapid heartbeat, irritability, shakiness, headache, and fainting.

Care will be taken to avoid these complications. An experienced research nurse will insert the IV under sterile conditions, and glucose levels are measured immediately, so if levels get too low, the test will be stopped and juice will be provided.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to reduce the possibility of this happening. See the section below titled: "What happens to the information collected for the research?".

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you or your insurance company. However, you or your insurance company will be responsible for costs related to your usual medical care.

What happens to the information collected for the research?

Study records that identify you will be kept confidential. Study records will be kept in a locked office and are only accessible by members of the research team. Data will be coded so that you are not identified and will not contain information that can identify you. The data collected in this study will be used for the purpose described in the form. Data from this study may be used in medical publications or presentations. Your name and other identifying information will be removed before this data is used. If we wish to use identifying information in publications, we will ask for your approval at that time.

Efforts will be made to limit the use and disclosure of your personal information to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution. The research team includes the individuals listed on this consent form and other personnel involved in this study at the Northwestern University and Rush University. As part of the study, Dr. Knutson and her research team may report the results of your study-related procedures and tests explained above to the National Institutes of Health (NIH). These include the information from the wrist activity monitor, the sleep recording and the questionnaires, as

well as your age, sex, ethnicity, height and weight. The information being sent will not contain any information that identifies you.

Plasma from blood samples and saliva samples collected during your laboratory session will be retained and stored either in the CRU at Northwestern or the Endocrinology Lab at the University of Chicago until primary analysis can be done, once analyzed they will be destroyed. All samples will be deidentified using only the study ID code. After the saliva specimens collected at home are assayed at Rush University by the co-investigator Dr. Helen Burgess, they will be destroyed. In this study, you will be asked about illegal activities or highly personal behavior. We have obtained a Certificate of Confidentiality from the federal government. However, we may still be required under certain circumstances to release your information.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include:

- You are unable to meet the requirements of the study;
- Your medical condition changes;
- If the study is stopped.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

If you become ill or get injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

<u>Payment</u>

If you agree to take part in this research study, we will pay you a total amount of $450 for completing the study.

- $50 for the screening, including both the sleep study (PSG) and the glucose tolerance test.

- $150 for the in-home assessment if all components are completed, including a minimum of 5 days of wrist activity monitoring, the saliva samples and the PSG sleep recording.
- $250 for the laboratory session, including the blood pressure monitoring, saliva samples and 5-hour glucose tolerance test.
- You will receive the amount indicated for each component if that component is completed as described.

Payment will be made by check and mailed out to you. The processing time is about 4-6 weeks after completion of the last inpatient visit. The Accounting Services at Northwestern University will be given your name, address, and Social Security Number in order to issue a check for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history including an mental health diagnosis
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- History of substance or alcohol abuse
- History of mental health disorders (e.g. depression, anxiety) including prescribed medications, doses, and length of use.

During this study you may be coming to a Northwestern Memorial Healthcare Corporation entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Rehabilitation Institute of Chicago (RIC), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH).

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy

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[except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited the Rehabilitation Institute of Chicago (RIC), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

However, Illinois law does not allow the re-release of HIV/AIDS, genetic testing, mental health and developmental disabilities information by the recievers of the information except in precise situations allowed by law.

Also, Federal Confidentiality Rules, 42 CFR Part 2, prohibit making any further disclosure of substance use disorder information unless further disclosure of this information is expressly permitted by written consent of the person to whom it pertains or as otherwise permitted by 42 CFR Part 2.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will expire at the end of the research study.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

Kristen L. Knutson, PhD
Center for Circadian and Sleep Medicine
Department of Neurology
Northwestern University Feinberg School of Medicine
710 N Lakeshore Drive, Room 523
Chicago, IL 60611

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Do not sign this consent if today's date is later than the stated expiration date above.

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	The researcher may contact me after I have finished participating in the study to clarify and ask questions about my responses to questionnaires and my performance on study activites.
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.
_____	_____	The researcher may retain any leftover blood or tissue samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to readily ascertain my identity.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent