Night Owl Metabolism

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JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Adolescents commonly develop delayed sleep schedules in normal development related to physiologic processes, turning into “night owls” (late chronotype). Youth-onset type 2 diabetes (YoT2D) is a disorder with fast progression and early complications. Delayed sleep timing has been identified as a possible modifiable risk factor for YoT2D. Although prior studies have linked shifted sleep timing to impaired glucose metabolism, these studies may not extrapolate to youth with late chronotype as they utilize standard morning testing with oral glucose tolerance tests (OGTTs), at a time mis-aligned to the typical schedule of an individual with late chronotype. As glucose tolerance worsens as the day progresses until the middle of the night in healthy individuals, testing at a time when youth with late chronotype are typically asleep may alter results and lead to potential mis-diagnoses. The goal of this study is to investigate whether alignment of glucose metabolic testing with chronotype improves glycemic outcomes and whether alignment of first morning meal timing to chronotype improves post-prandial glycemic response in youth with late chronotype. The proposed study uses a novel and rigorous randomized cross-over study design in youth (18-23y) with late and non-late chronotype (n=35 per group) to assess the glycemic effect of “aligning” an OGTT or first-meal of day to a subject’s chronotype. Both groups will undergo 2 OGTTs (aligned and mis-aligned with chronotype) to compare glucose tolerance and insulin sensitivity within-subject (primary outcome) and between groups (Aim 1). Then, youth will also undergo two standardized meals (aligned and mis-aligned with chronotype) while wearing continuous glucose monitoring to compare postprandial glucose excursions within-subject and between groups (Aim 2). A pilot Exploratory Aim 3 (n=12 per group) will investigate delayed melatonin patterns under dim-light as a potential pathophysiologic mechanism behind abnormal glucose tolerance in youth with late chronotype on morning OGTTs. This study has potential implications for both clinical and research practices, as well as meal timing recommendations.

2. Objectives (include all primary and secondary objectives)

This study has two main objectives with an additional exploratory third objective:

Aim 1: To compare morning vs. midday glucose tolerance and insulin sensitivity (IS) (analyzed by OGTT Minimal Model) in youth with late chronotype (primary analysis) and non-late chronotype, using OGTT in a controlled lab setting.

Aim 2: To compare morning vs. midday first-meal of day standardized mixed meal glycemic responses in youth with late chronotype (primary analysis) and non-late chronotype, using continuous glucose monitor (CGM) in a real-world setting.

Exploratory Aim 3: To examine a possible role of melatonin in misalignment-induced glucose intolerance.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The proposed study is based on preliminary data from 2 years of research funded by an Administrative Supplement on NIDDK R01DK115648, "Cardiometabolic Health in Adolescents of South Asian Ancestry- the CHAriSmA study" (PI: Dr. Sheela Magge). The parent R01 compares cardiovascular risk factors (including using OGTT and oral Minimal Model) between South Asian, African American, and White adolescents aged 12-21y. A subset of the parent study participants measured 15d of actigraphy along with sleep diaries (text-messaged twice daily) in order to examine the cross-sectional relationships between glucose metabolism with sleep duration and sleep timing. In the 43 participants analyzed (out of 63 participants recruited over the course of 21 months, an average 3 participants per month), the cohort was (median (IQR)): age 20.2y (18.6-21.4), 49% female, BMI 25.8 kg/m$_2$ (24.1-28.6), baseline HbA1c 5.0% (4.9-5.3).

Actigraphy measures demonstrated (median (IQR)): normal young adult sleep duration 7.5 hours (6.8-8.1), minimal social jetlag (difference between weekend and weekday sleep onset) 37.4 minutes (-13.4, 84.7), and delayed sleep onset 1:00AM (12:02AM-1:48AM) with 21% after 2AM. When adjusting for BMI, participants with later sleep timing had significantly higher OGTT 2-h glucose (for every hour later in habitual sleep onset, 2-hr glucose was 7.4 mg/dl higher), reduced IS (by 28.5% for each hour later in sleep onset), and higher insulin incremental area under the curve (iAUC). Based on these results, a 4-h difference in bedtime would equate to a clinically significant ~30 mg/dL difference in 2-h glucose on a morning OGTT. In addition, 8 (19%) research participants had impaired glucose tolerance (IGT), and youth diagnosed with IGT had later sleep onset than youth with normoglycemia. Each hour later of delayed sleep onset was associated with a 3.3x greater odds of being diagnosed with IGT.

Sleep duration was not associated with any glycemic outcomes and all analyses remained significant when adjusting for obstructive sleep apnea (OSA) risk (screened using Berlin Questionnaire and Sleep-Related Breathing Disorder scale). We concluded that youth with late sleep timing had glucose intolerance and reduced IS on a morning OGTT (median (IQR) timing of OGTT: 9:34AM (9:18AM-9:49AM)). However, we do not know if this glucose intolerance would be resolved by aligning OGTT timing to chronotype or how this data corresponds to glucose ingestion in real world settings.

Additional preliminary data pertinent to the proposed aims include a prior project evaluating the relationship between sleep duration with glycemic control by hemoglobin A1c (HbA1c) (primary analysis) and glycemic metrics by CGM (secondary analysis) in adolescents with youth-onset type 2 diabetes. This project provided me with skills in the use of actigraphy and CGM in clinical research and confirmed the commonality of late chronotype with delayed sleep onset (median (IQR): 1:40AM (12:22AM-2:32AM)) in an adolescent population (median (IQR) age 15.6y (14.2-17.5)).

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Overall Study Design: This project will use a randomly ordered paired 2-group cross-over design. Aims 1 and 2 use complementary methods to assess in-lab (OGTT) (Aim 1) and real-world (CGM monitoring following a standardized meal) (Aim 2) glucose metabolism at different times of day. Sleep data via actigraphy will be gathered prior to the first OGTT to assess normal routine patterns. In Aim 1, all participants (total n=75, ideally n=35 usable data in each chronotype group, 5 additional participants recruited to account for potential dropout rate) will wear actigraphy for sleep measures over the Aim 1 period and will be randomized to start with either late (12:30PM) or early (8:30AM) OGTT and then undergo the opposite timing, allowing for at least a 1-week washout period between OGTTs. After Aim 1 procedures, at least 1 week without procedures will be allowed for wash-out before beginning Aim 2. In Aim 2, participants will again wear actigraphy as well as CGM for real-world glucose monitoring, and then will be randomized to start with either a late (12:30PM) or early (8:30AM) first-meal of day standardized meal shake and then have the opposite meal timing with at least a 1-week washout period in between. After completion of Aims 1-2, a subset (total n=24, n=12 per chronotype group) will undergo Exploratory Aim 3, with dim-light melatonin measurements per published procedures in prior studies. If any part of the study procedures has technical issues or was not completed correctly, the study procedure may be repeated and could be in a different order or timing if other procedures were completed appropriately. Additional payment for any parts redone can be added per PI discretion.

All procedures described are for research purposes only:

1. Pre-screening Visit (Virtual or In-Person): We will obtain a medical history, weight/height, and self-reported sleep patterns as outlined by the telephone screening script. If the participant appears to be eligible, we will continue into the consent and screening visit process. If the participant is not eligible, they can give us permission to contact them at a later date if they become eligible.

2. Screening Visit (Virtual or In-Person): After obtaining informed consent, the participant will complete 2 screening questionnaires to confirm eligibility: (1) one questionnaire to gather information on OSA risk (Berlin Questionnaire (validated in adults)). Those who screen high-risk for OSA or who have insufficient typical sleep duration (<7 hours) or excess social jetlag (>2 hours) will be ineligible and (2) Alcohol Use Disorders Identification Test (AUDIT). Eligible participants will be mailed or delivered an actigraphy watch by the courier service (or given if visit performed in person). The subject will be randomized and OGTT visits will be scheduled.

3. Start of Aim 1 Visit (Virtual or In-Person): We will plan this study visit during a time that is routine for the participant that aims to be a time without holiday or vacation schedules within the subsequent 2 weeks. During this visit, the study coordinator will review the study plan for Aim 1 with the participant including dates of visits, instructions for fasting prior to the OGTT (at least 8-h the night prior to the test), and advise the subject to follow a typical carbohydrate diet (≥ 150g of carbohydrate per day), a ≥ 50g meal the night

before the test to avoid false positive results seen in prior studies, and limit exercise prior to the OGTT. The study coordinator will instruct the participant to start wearing the actigraphy watch on their non-dominant wrist. The twice-daily REDCap text-message based sleep diary will start before the OGTT #1 Visit.

4. OGTT #1 Visit: All participants from both chronotype groups will be randomized to receive the Early (8:30AM) or Late (12:30PM) OGTT first. At placement of blood-drawing IV, a HbA1c level will be drawn. OGTT will start with an oral glucose load (1.75 g/kg; max of 75 g) ingested over 2 minutes (at time = 0) and will last 2-h with 9 samples drawn at timepoints (min: -5, 0, 10, 15, 20, 30, 60, 90, 120) for measurement of glucose, insulin, and c-peptide. At each timepoint, glucose will be measured via a glucometer. At the visit, if timing allows, we will also conduct anthropometrics measurements and questionnaires to gather chronotype and social jetlag (Munich chronotype and Morningness-Eveningness Questionnaire), family history, medical history, birth history, and medication list.

5. OGTT #2 Visit (In-Person): The second OGTT will occur at least 7d after OGTT #1. If the previous OGTT #1 was completed earlier or later due to unexpected issues, the OGTT #2 will follow similar schedule changes but maintain a washout period of at least 7d OGTTs. All participants will perform the OGTT that they did not previously perform (Early - 8:30AM or Late - 12:30PM). If not complete at OGTT #1, and timing allows, we will also conduct anthropometrics measurements and questionnaires to gather chronotype and social jetlag (Munich chronotype and Morningness-Eveningness Questionnaire), family history, medical history, birth history, and medication list.

6. CGM Visit, Start of Aim 2, after OGTT #2 visit (Virtual or In-Person): We will aim to plan this visit during a routine time for the participant without holiday or vacation within the subsequent week. Participants will come in to be provided a second actigraphy watch, a CGM sensor, and standardized meal shakes. The placement of CGM will be done with the participant by research team. Participants will be instructed to eat and sleep on their typical patterns during this time except for days of standardized meals. During this visit, the study coordinator will review the Aim 2 study plan with the participant including dates and times of standardized meal timing and advise the participant to fast for at least 8-h prior to the scheduled time of the standardized meal. The participant will be instructed to start wearing the actigraphy watch on their non-dominant wrist and in the study team will place the CGM sensor. The twice-daily text-message based sleep diary will initiate with 1st sleep diary sent on the following morning after this visit. If not complete at either OGTT, we will also conduct anthropometrics measurements and questionnaires to gather chronotype and social jetlag (Munich chronotype and Morningness-Eveningness Questionnaire), family history, medical history, birth history, and medication list.

7. Standardized Meals (no visit): Participants will be given Boost Plus meal-replacement shakes at the CGM visit. During Aim 2, standardized meals will be ingested twice as first-meal of day (fasting until meal) at least 7d apart. Participants will be asked to consume their meals within 30 minutes and limit their physical activity around the meal.

8. Dim-light Melatonin Measurement Visit (In-Person): A subset of participants (n = 12 per chronotype group) will be admitted to a dimly lit (<4 lux), temperature-controlled room and will undergo dim-light melatonin onset (DLMOn) and dim-light melatonin offset (DLMOff) assessment using salivary collection per published procedures. The saliva collection will begin 4-6h before average habitual bedtime and continues at regular

intervals until a2-6h after average habitual bedtime at which point participants will be allowed to sleep. DLMOn will subsequently be calculated as the interpolated time point at which melatonin concentrations cross and maintain above 3 pg/mL, rounded to the nearest half-hour. Participants will be awakened and melatonin measurement will re-start at 2-4h before average habitual wake-up with regular interval saliva sampling. When samples are collected, participants will fill out a survey on how they feel at the moment as it may change interpretation of result. DLMOff will be defined as the linear interpolated time point at which melatonin concentrations cross and maintain below 3 pg/mL.

Procedures Ongoing during Aims 1 and 2:

1. Actigraphy (Aim 1, Aim 2): The ActiGraph GT3XP-BTLE 4GB Activity Monitor, a watch-like device, is a research-grade triaxial accelerometer, that reliably measures duration, onset and offset of sleep. Participants will be asked to wear the ActiGraph watch on their non-dominant wrist twice: during Aim 1 and Aim 2 delivered back in a provided pre-paid USPS box,courier service, in-person.

2. CGM Monitoring (Aim 2): A CGM sensor (Dexcom G6 Professional CGM) will be placed in-person on the participant's abdomen on Start of Aim 2 virtually or In-person. The process of CGM placement will be reviewed in person at CGM visit. Participants will wear the CGM for up to 14 days (blinded) during Aim 2, and then will return it via a provided pre-paid USPS box,courier service, or in-person. The CGM collects glucose data every 5min.

3. Text-Message Based Sleep Diary: A sleep diary will be sent via text-message twice daily to all participants during both Aim 1 and Aim 2. Questions include self-reported timing of sleep, sleep latency, awakenings, sleep quality, and periods of actigraphy non-wear to aid in actigraphy analysis. Questions also assess caffeine intake, use of sleep aids, screen time use, irregular schedules, meal timings, snack timing, alcohol intake, and exercise.

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. n/a

c. Study duration and number of study visits required of research participants.

Participants will be enrolled in the study until all procedures have been completed (up to 12 months if participating in all aims (including Aim 3 DLMOn/DLMOff), up to 6 months if only participating in Aims 1 & 2). Participation in Aims 1 & 2 involves 1 screening visit,1 study-start visit, 2 in-person OGTT visits, and one CGM placement in-person or virtual visit. Participation in Aim 3 involves an additional overnight in-person visit.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

For randomization in Aim 1, participants will be assigned to Early or Late OGTT for the first visit with crossover to the alternate for the second visit (Fig 1). Randomization will be done via a computer-generated random number list prepared by the statistician who will have no clinical involvement in the study. The list will then

be provided to the study coordinator. The investigator will not be masked to assignment for Aim 1 as they will be available during OGTT testing as needed. In Aim 2, participants will be assigned to Early or Late standardized first meal with crossover to the alternate for at least 7 days afterwards. Randomization will be done via a computer-generated random number list prepared by the statistician who will have no clinical involvement in the study. The list will then be provided to the study coordinator, and the investigator will be blinded to randomization. If determined necessary by the study team to re-do any study procedures for technical errors, statisticians will be consulted to determine need for re-randomization and their recommendation will be followed.

e. Justification of why participants will not receive routine care or will have current therapy stopped. n/a

f. Justification for inclusion of a placebo or non-treatment group. n/a

g. Definition of treatment failure or participant removal criteria.

Participants may be removed from the study if, in the opinion of the study team, continued participation would cause harm to the participant or if they fail to comply with study procedures.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

n/a

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

Blood collected during the OGTTs will be used to measure glucose, insulin, and c-peptide, which will be used to calculate measures of glycemic control and variability. Fasting blood samples will also be used to measure hemoglobin A1c. If blood samples remain after these planned analyses, they will be stored for future research. Participants in Exploratory Aim 3 (DLMOn/DLMOff) will also generate saliva samples, which will be analyzed for salivary melatonin levels. These results will be used to calculate DLMOn and DLMOff times.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age 18-23 years
- Overweight per adult CDC guidelines BMI: 25-30
- Post-puberty per participant report
- Normal sleep duration (estimated average >7 hours per night)
- Social jetlag < 2hours, per participant report

Exclusion Criteria:

- Known diabetes, sleep disorders, or pregnancy and/or known major organ system illness or genetic syndrome that can affect glucose metabolism or sleep

- Medication or substance use known to affect insulin sensitivity, glucose tolerance, sleep or circadian rhythm if cannot be withheld without ongoing effects during time period of study procedures
- High risk for OSA, per questionnaire
- Overnight or rotating shift work that can impair consistent sleep patterns or is not aligned with preferred sleep patterns
- Unable to read/write in English, as questionnaires are only validated in English
- Unwilling or unable to provide informed consent or assent
- Active eating disorder that would interfere with study protocol
- Illicit drug usage
- Pregnant or lactating female
- Parent/guardian of child(ren) who may disrupt sleep
- Of note, participants who have travelled across time zones must have adequate time to recover from jet lag prior to enrollment (i.e., at least 3 days per time zone).

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Dexcom G6 Pro Continuous Glucose Monitors: Continuous glucose monitors (CGMs) are minimally invasive, single-use devices that are applied to the skin and continuously measure interstitial glucose for up to 10 days, thereby potentially revealing more dysglycemia than a time point (OGTT) or average (hemoglobin A1c). CGMs are approved for use by people with diabetes to monitor trends in glucose and make real-time decisions about diabetes management. Professional CGMs are also approved to assess glycemic variability in the home environment in individuals over age 2 without diagnosed diabetes. The Dexcom G6 Pro CGMs will be used in blinded mode, so participants will not be able to see their glucose measurements.

ActiGraph wGT3X-BT: The ActiGraph wGT3X-BT is a research-grade FDA-cleared tri-axial accelerometer used to measure activity. When used in combination with ActiGraph algorithms, the data can be used to estimate sleep timing and duration. Participants will be blinded to actigraphy results.

7. Study Statistics

a. Primary outcome variable.

The primary outcome variables for each study aim are listed below:

Aim 1: Within-subject difference in 2-h glucose between Early and Late OGTT in late chronotype group

Aim 2: Within-subject difference in 2-h post-prandial incremental area under the curve of glucose between Early and Late Meal in late chronotype group

Exploratory Aim 3: Relationship between DLMOff and morning OGTT 2-h glucose and insulin sensitivity

b. Secondary outcome variables.

Secondary outcome variables for each study aim are listed below:

Aim 1:

- Within-subject difference in insulin sensitivity between Early and Late OGTT in late chronotype group
- Within-subject difference in insulin secretion indices between Early and Late OGTT in late chronotype group
- Within-subject difference in fasting glucose between Early and Late OGTT in late chronotype group
- Within-subject difference in incremental area under the curve of insulin between Early and Late OGTT in late chronotype group
- Within-subject difference in disposition index between Early and Late OGTT in late chronotype group
- Within-subject difference in insulin clearance between Early and Late OGTT in late chronotype group
- Between-group differences in all above primary and secondary outcome variables as well as HbA1c

Aim 2:

- Within-subject difference in 2-hour post-prandial peak between Early and Late Meal in late chronotype group
- Comparison between chronotype groups of all primary and secondary outcome variables as well as mean glucose, percent time spent above 120 mg/dL, percent time spent above 140 mg/dL, number of excursions greater than 140 mg/dL, standard deviation of glucose, and coefficient of variation of glucose

Exploratory Aim 3:

- Relationship between melatonin level at 8:30 AM and morning OGTT 2-h glucose and insulin sensitivity
- Relationship between dim-light melatonin onset (DLMOn) and morning OGTT 2-h glucose and insulin sensitivity
- Comparison between chronotype groups of DLMOff and morning melatonin level

c. Statistical plan including sample size justification and interim data analysis.

Statistical Plan for Primary Analysis in Aim 1: A unified approach based on mixed effects general linear modeling (meglm, STATA 17) will be pursued. This approach enables analysis to account for dependencies owing to use of “own controls” and to overcome the issue of outcomes that do not initially meet normality and homoscedasticity assumptions. Initially, meglm models separately applied to each chronotype group will include main and interactive effects of intervention and intervention order (early-late or late-early). The interaction effect will only be retained

if it reaches statistical significance. For Aim 1, the primary analysis will evaluate the within-subject difference in the late chronotype group between Early OGTT and Late OGTT in 2-h glucose (primary outcome), IS, and other insulin secretion and clearance metrics. The above modelling approach will allow us to adjust variance estimates to account for the aforementioned dependencies in the data.

Statistical Plan for Primary Analysis in Aim 2: For Aim 2, the primary analysis, will, as above, use a mixed effects general linear model comparable to Aim 1 to estimate in the late chronotype group the within-subject difference in 2-h iAUC of glucose (primary outcome) and post-prandial glucose peak between Early Meal and Late Meal. Similar models will be utilized for advanced comparisons of sleep and glycemic excursions (lme4 package, R).

Aims 1 and 2 Secondary Analysis: Importantly, secondary analysis will examine differences between chronotype groups in Early vs. Late Meal and Early vs. Late OGTT testing in regard to Aim 1 and 2 outcomes. These analyses will control for differences in age, sex, BMI, race/ethnicity, sleep duration, and work/education status, and sensitivity analyses will also be stratified by sex. Should use of integrated transformations, through link functions, fail to meet model assumptions, analysis can shift to comparing median levels to relax assumptions.

Statistical Plan for Aim 3: Regression modeling will be used to evaluate evidence in pooled group comparisons that DLMOff predicts 2-h glucose and IS on Early OGTT. Secondary analysis will evaluate the association between melatonin level at 8:30AM (timing of Early OGTT) and DLMOn with OGTT outcomes. Pooling data from both aligned and mis-aligned participants will evaluate the full spectrum of the relationship between circadian metrics and morning glucose responses. DLMOff will be compared between groups by T-test or equivalent.

Sample size and Power Calculations: G*Power was used to develop sample size estimates to detect clinically meaningful effect size differences. Based on a 2-tailed type 1 error of 0.05 in own-control comparisons, a sample size of n=35 per chronotype group (total n=70) provides >90% power to detect effect size difference of 0.6 between paired means. A sample size of 35 per group was also determined to have 80% power to detect a 0.65 effect size difference in independent, between-group comparisons assuming a 1-tailed test and type 1 error of 5%. Based on these estimates, the study is adequately powered to detect clinically meaningful effects for study aims and hypotheses. We are updating the sample size to include 5 additional participants to provide a buffer for up to 7% dropout rate, increasing the sample size to n=75. In Exploratory Aim 3, a sample size of n=24 will allow the study to estimate the strength of relationship as r_2 +- 95% CI between 2-h glucose or IS and DLMOff. It will demonstrate feasibility to measure and the potential relationship between circadian metrics and metabolic outcomes to support future hypotheses.

d. Early stopping rules.

If the Hopkins/Affiliates faculty/staff member designated to periodically review adverse events raises concern for need to stop early, then study investigators will review available data and make decision regarding stopping early.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
b. Steps taken to minimize the risks.
c. Plan for reporting unanticipated problems or study deviations.
d. Legal risks such as the risks that would be associated with breach of confidentiality.
e. Financial risks to the participants.

Questionnaires, Health History and Anthropometric Measures: These procedures acquire information that is routinely collected in the process of medical care of patients. There are not any significant physical risks from these procedures. As with all medical information, there is always the risk of psychological distress if personal health information is not held confidential within the wishes of the participant.

Phlebotomy & multiple blood sampling: The blood volume collected during OGTT will be approximately 200mL per OGTT. The blood volume removal is much less than the maximum blood volume removal per 8-week period recommended by OHRP (Adults < 10.5 mL/kg or 550 ml, children < 7mL/kg).

There is a risk of bruising and discomfort at the venipuncture site. Blood draw may result in temporary discomfort from needle stick, bruising, fainting, weakness, and rarely an infection at the site. These risks of complication will be mitigated with standard sterile technique and staff experienced performing phlebotomy.

OGTT: Beyond the blood sampling concerns described above, the risks for OGTT include temporary high or low blood sugar and upset stomach.

The OGTT is frequently used to screen for diabetes and impairments in glucose regulation in children both within the confines of a study and in routine clinical practice; additional intermediate blood draws will be performed for glucose, insulin and c-peptide in order to assess insulin sensitivity. Because of these intermediate time points for blood collection, an intravenous line will be placed, which can be associated with discomfort and a small risk of infection. Experienced research nurses will perform the OGTT in the Outpatient JHU ICTR facilities; OGTT are routinely performed in this setting. Nine blood samples are required and the volumes of blood will be minimized to reduce the risk of anemia.

There is a small and rare risk of an upset stomach when drinking the sugar drink. The participant will need to fast overnight prior to the OGTT which may cause an upset stomach, a headache, or light-headedness. These symptoms are occasional but not serious. The major risk of the oral glucose tolerance test is hypoglycemia. Hypoglycemia is reported in 20-25% of otherwise healthy individuals who undergo oral glucose tolerance testing. Subjects will be closely monitored during studies by personnel with experience in managing hypoglycemia and its associated problems. Portable glucose meters will be used to allow rapid detection and prompt treatment of hypoglycemia. Plasma glucose levels will be measured at the scheduled intervals. In addition, blood glucose levels will be measured (from blood drawing IV or by fingerstick) at any time during the study if symptoms of hypoglycemia occur (such as tremors, sweating, and irritability). Subjects will be treated with oral glucose supplementation (e.g. orange juice) if symptomatic. Blood glucose will be monitored until normalization is assured.

CGM: CGM use has a low risk of causing discomfort, skin irritation under the adhesive, bleeding or bruising at the insertion site. There is a small risk of infection. This may

cause moderate redness, pain or swelling. Participants will be advised to use standard sterile technique when the CGM is placed (during the start of Aim 2 visit). If a participant has an adverse reaction in the form of irritation, infection or discomfort at the CGM insertion site, the study investigator will evaluate and manage the reaction. A CGM provides a continuous reading of blood sugars 24 hours a day, which can feel like a lot of information. In order to minimize anxiety in this population of overweight young adults, participants will be blinded to the readings, and the data will be downloaded by the study team after the period of wear.

Standardized Meal: The meal timing intervention (differing first-morning of day meal time) poses minimal risk. Potential adverse effect of the intervention may include participants' dislike of the food provided.

ActiGraph: Risks associated with ActiGraph use are minimal, and mainly consist of risk of skin irritation from the band of the device. Watch bands will be sanitized between uses, and participants will be advised to remove the device in the event of skin irritation. Participants will be blinded to all actigraphy data and may also find it inconvenient or uncomfortable to wear the activity monitor on their wrist.

DLMOn/DLMOff: Like any sleep study, the DLMOn/DLMOff procedure may result in sleep that is less restful than a participant's typical at-home sleep, due to discomfort in the lab environment and monitoring equipment. Only a subset of study participants will undergo DLMO/DLMOff, and those who elect to participate may terminate their participation at any time.

Legal risks, including loss of confidentiality, will be mitigated with use of unique study identifiers, IRB-approved staff, locking up paper records and utilization of Johns Hopkins approved servers for data containing protected health information. Any publications derived from study will not identify subjects in any way. However, participation in research may lead to unintentional loss of privacy.

Financial Risks: There are no anticipated financial risks to participants.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There is no direct benefit to the participants, but the findings from this study may help others in the future

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants may earn up to $1,050 if they complete all study procedures including Aim 3, or up to $550 for completing only Aims 1 & 2, according to the schedule outlined below:

Procedure	Compensation
Aim 1:	
OGTT 1 Completion	$150
OGTT 2 Completion	$75
Watch Returned	$25
Half of Data Present on Watch and Sleep Diary	$25
Additional Bonus for Full Data on Watch and Sleep Diary	$50
Maximum total for Aim 1	$325
Aim 2:	
Placement of CGM Completion	$25
Watch Returned	$25
CGM Returned	$25
Half of Data Present on Watch and Sleep Diary	$25
Half of Data on CGM	$25
Boostplus Meal 1 Consumed Appropriately	$25
Boostplus Meal 2 Consumed Appropriately	$25
Additional Bonus for Full Data on Watch/Sleep Diary/CGM	$50
Maximum total for Aim 2	$225
Aim 3 (substudy):	
DLMOn/DLMOff	$500
Maximum total for Aim 3	$500
Maximum Compensation	$1,050

Compensation is sufficient to cover the costs of parking.

11.

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The cost of all study procedures and devices will be paid for by the study.

12. Transfer of Materials

Transfer of biospecimens from Johns Hopkins to another organization for research purposes and receipt of biospecimens from an outside organization for your research must adhere to JHU policies for material transfer (https://ventures.jhu.edu/faculty-inventors/forms-policies/) and biospecimen transfer (https://hpo.johnshopkins.edu/enterprise/policies/176/39187/policy_39187.pdf?_=0.622324232879). n/a