Title: Effect of long term sleep restriction on energy balance

NCT number: NCT02960776

Date: 03/28/2024

Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAQ7746(M00Y09)	**Protocol Status:**	Approved
Effective Date:	02/05/2024	**Expiration Date:**	02/04/2025
Originating Department Code:		MED Obesity (752060X)	
Principal Investigator:		St Onge, Marie Pierre (ms2554)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Impact of sleep restriction on performance in adults		
Protocol Version #:	Y1M1-Adm Suppl	**Abbreviated Title:**	NIH Sleep Restriction
Was this protocol previously assigned a number by an IRB:		No	

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?
No

IRB Expedited Determination

8. Continuing review of research previously approved by the convened IRB as follows: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

Renewal Information

Enrollment status:
Closed to further enrollment: remaining research activities are limited to data analysis only
Provide any additional information necessary to explain the study status:
No participant was enrolled or accrued in the last period and none are planned in the upcoming renewal period. This study is only open for data analyses and reporting.
Since the last renewal:
Have there been any changes in the relevant literature that would affect the study design or procedures?
No
Have there been any interim findings associated with this study?
Yes

Please Describe:
We have published data on lipid profile and inflammatory markers. Paper in press on cognitive function.

Have there been any publications resulting from this study?
Yes

Please Describe:
Barragán R, Zuraikat FM, Cheng B, Scaccia SE, Cochran J, Aggarwal B, Jelic S, St-Onge M-P. Paradoxical effects of prolonged insufficient sleep on lipid profile: A randomized trial. JAHA 2023 Oct 10:e032078D. PMID:37815115.
Zimmerman ME, Benasi G, Hale C, Yeung LK, Cochran, Brickman AM, St-Onge M-P. The effects of insufficient sleep and adequate sleep on cognitive function in healthy adults. Sleep Health, in press.

Have any participants been enrolled using the Short Form process?

No

Is there a Data Monitoring Committee (DMC), Data Safety Monitoring Board (DSMB), or other monitoring entity for this study?

No

Is an annual Progress Report required by the funding organization or coordinating center for this study?

No

Does this submission include a modification?

Yes

Provide a description of, and explanation for, all changes being proposed in this submission:

Personnel not involved in data analyses or reporting have been removed.

Indicate which sections of the Rascal submission are affected by the proposed modification. Each marked section must be revised as part of this submission:

[ ]General Information
[ ]Attributes
[ ]Background
[ ]Exempt and Expedited
[ ]Funding
[ ]Locations
[x]Personnel
[ ]Privacy and Data Security
[ ]Procedures
[ ]Recruitment/Informed Consent
[ ]Research Aims and Abstracts
[ ]Risks/Benefits/Monitoring
[ ]Subjects
[ ]Attachments (including Rascal-generated attachments)
[ ]No revisions to submission content required

Has the Investigator's Brochure (IB) or Device Manual been revised in this submission?

No

Has the consent form been revised in this submission?

No

Does this submission include a report of a protocol violation?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)
[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)
[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

No

Please indicate if any of the following University resources are utilized:

[ ] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)

[x] CTSA-Irving Institute Clinical Research Resource (CRR)

[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)

[ ] None of the above

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Chronic Sleep Restriction (SR) is highly prevalent in today's modern society [1]. Artificial light, portable electronic devices, and 24-h services have allowed individuals to remain active throughout the night, leading to reductions in sleep duration. SSD has been linked to obesity and our laboratory has been interested in establishing whether sleep could be a causal factor in the etiology of obesity. Given the increasing prevalence of obesity over the past 5 decades, coinciding with the marked reduction in sleep duration [2], further exploration into the role of sleep as a risk factor for obesity could provide additional ammunition in the fight to prevent further increases in the incidence of obesity. Currently, the prevalence of obesity is approximately 33% in 20-39 y-olds and 37% in 40-59 y-olds [3]. It is well known that obesity is associated with an increased risk of type 2 diabetes and cardiovascular disease (CVD), along with other debilitating diseases including orthopedic problems, cancer, and dementia. Those associated disorders are accompanied by high healthcare costs, as well as reduced productivity [4]. Furthermore, our target population (adults age 20-40 y) is within the adult age range with the lowest prevalence of obesity, precedes the age range with highest prevalence of obesity [3], and is the one with the most striking association between SSD and obesity [5,6]. Our current state of knowledge surrounding the relationship between SSD and obesity stems largely from cross-sectional studies: short sleepers have a higher BMI than normal sleepers and have higher odds of obesity [7, 8]. Longitudinal studies also point to an increased risk of large weight gain over time in short sleepers relative to normal sleepers [9-11]. However, those studies cannot infer causality and are fraught with limitations such as self-report of sleep duration, which could lead to bias. Only two longitudinal studies have objectively measured sleep duration with actigraphy, and those have not found any association between SSD and weight gain over time [12, 13]. Of note is that one of those studies was performed on women who were 48-59 y old at baseline [12], an age range in which sleep duration is less closely related to obesity risk. In the proposed study, the target population will be <40 y, an age group identified as being at highest risk of large weight gain with sustained short sleep [14]. Given the cross-sectional evidence of an association between SSD and obesity, from both questionnaire and actigraphy assessments of sleep, investigation of possible causal relationships is warranted. Capers and colleagues recently published a meta-analysis concluding that no studies exist to assess the effects of long-term manipulation of sleep duration on obesity risk [15]. They further "call for additional research using more standardized methods and measures, as well as evaluations of associated outcomes with sufficient sample sizes and duration to ascertain whether a causal relationship truly exists

between sleep duration and body weight regulation". This will be fulfilled should the proposed study be funded. Clinical intervention studies, on the other hand, have consistently shown that SR increases EI in normal sleepers [16-19] above and beyond the added cost of waking EE [20]. Criticisms of these studies are that they have employed short intervention periods, ranging from a single night to 14 d, and have tested very restrictive sleep schedules, typically 3 h less than Habitual Sleep (HS) (4-5.5 h TIB). Although these studies provide information on causality, many questions remain unanswered: Does longer, milder SR as observed in individuals with SSD, lead to positive energy balance (Aims 1 & 2)? Is the increased EI observed in acute studies maintained over time and if so, does it result in increased adiposity (Aim 1) and adverse cardiometabolic risk profile (Aim 3)? The proposed study will answer these critical questions.

In addition to being a risk factor for cardiovascular disease, type 2 diabetes, and obesity [21], short sleep duration (SSD) is related to an increased risk of cognitive impairment in older adults [22,23]. Individuals at lowest risk of cognitive impairment are those with adequate sleep duration of 7-8 h/night [22]. SSD may induce cognitive impairment in older adults by promoting Alzheimer's disease pathology directly. Indeed recent studies showed that inadequate sleep is associated with Alzheimer's disease biological markers, including cerebrospinal fluid measures of beta amyloid and measures of fibrillar amyloid derived from positron emission tomography (**PET**) [24]. Intervention studies demonstrated increased circulating plasma levels of amyloid beta in young adults [25] and increased fibrillar brain amyloid beta in older adults [26] following one night of sleep deprivation. However, there are no studies to date that have evaluated the impact of long-term, sustained short sleep duration, mimicking the widespread sleep behavior of U.S adults, on cognitive function in older adults, and the mediators and moderators of the effect of sleep deprivation on cognitive outcomes are poorly understood. The proposed supplementary study examines the effect of sleep restriction on cognitive outcomes in older adults and tests the possibility that cerebral atrophy, cerebrovascular disease, and hormonal markers mediate this effect.

The currently-funded *Sleep Restriction Study* (R01 HL128226, PI: St-Onge) provides an ideal opportunity to measure changes in cognition in cognitively normal young and older adults undergoing SR. The protocol enrolls young adults, normally sleeping 7-9 h/night, into a randomized controlled trial of 2 intervention periods of 6 wk each, differing in the length of the sleep episode: either habitual sleep (HS) or habitual sleep minus 1.5 h (SR). The main objective of the parent study is to evaluate the impact of SR on energy balance regulation and explore a mechanism via alterations in hormonal and metabolic markers. The proposed supplement seeks to incorporate a neuropsychological evaluation to the current application; recruit a group of older adults (age range 55-75 y) with normal sleep function; and collect magnetic resonance imaging (MRI)-derived measures of brain atrophy (volumetry and cortical thickness in Alzheimer's disease -related regions) and cerebrovascular disease (white matter hyperintensities) into the ongoing crossover study. In this project, we will assess whether SR challenges acute cognitive outcomes in older and younger adults (Aim 4), whether these effects are moderated by brain atrophy and small vessel cerebrovascular disease (Aim 5), and if changes in metabolic or hormonal profiles mediate changes in cognitive function as a result of SR (Aim 6).

References:

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Study Design:

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

We propose a randomized, crossover, outpatient sleep restriction study with 2 phases of 6 wk each. Sixty -six men and pre-menopausal women, age 20-40 y, BMI 20-34.9 kg/m2, who have at least one parent with BMI >27 kg/m2 (if participant BMI is 20-24.9 kg/m2), will be recruited from the New York City area. Participants who will be recruited to participate in this study will habitually sleep 7-9 h/night, will be free of any current and past sleep and psychiatric disorders, including eating disorders, and will not have diabetes or CVD. The sleep durations will be the participant's regular bed- and wake-times during the habitual sleep (HS) phase and HS minus 1.5 h in the sleep restriction (SR) phase. During the HS phase, participants will be asked to follow a fixed bedtime routine based on their screening sleep schedule. During the SR phase, participants will be asked to keep their habitual wake time constant but delay their bedtime to achieve a reduction of 1.5 h in total sleep time. Two weeks prior to randomization and during washout periods, participants will wear an actigraph (Micro Motion Logger Sleep Watch, Ambulatory Monitoring, Inc., Ardsley, NY) and keep a sleep diary to verify sleep duration and sleep-wake schedule. In addition to achieving an average sleep of 7-9 h/night, per wrist actigraphy, participants will only be enrolled if they achieve 7 h of sleep for at least 10 of the 14 nights of screening and have <4 nights with <6 h of sleep. At randomization, a urine pregnancy test (for women) and drug screen will be performed. Participants will be asked to abstain from caffeine and alcohol intake for 24 h prior to the start of each study phase. Between study phases, if participants have not returned to baseline sleep patterns, an additional 2-4 wk washout period will be provided. In general, washout periods will be 6 wk in duration. This washout length enhances the likelihood that women will be in the same phase of their menstrual cycle at the start of each experimental phase. On the first day of each study phase (baseline), participants will come to Irving Center for Clinical and Translational Research (CTSA) at Columbia University in the morning after an overnight, 12-h fast. Participants will have anthropometric measurements taken, will provide a fasting blood sample, and will then be taken to the department of Radiology to undergo MRI scanning to assess body composition. Participants will begin the fixed bedtime routine that night. These baseline measurements will be repeated at endpoint, 6 wk later. Body weight and waist circumference will be measured weekly, fasting blood and urine samples will be taken at baseline, week-3, and endpoint, during adherence check visits. Brain responses will be assessed using two fMRI paradigms (resting state and task-based) at wk 6, 1 h before the participant's self-reported usual dinner time. The resting state paradigm and intrinsic functional connectivity (iFC) analysis will assess treatment effects on reward and interoception-related neuronal circuitry. During the resting state scan (2 runs, each ~ 5 mins), participants will focus on the fixation cross in the center of the screen. Wakefulness and compliance with eyes-open instructions will be monitored via an eye-tracking camera and verbal reminders given before every run. Pulse and respiration rates will be measured using MRI-compatible non-invasive physiological monitoring equipment. Food intake will be assessed at baseline, wk 3, and wk 6 by 3-d food records (2 weekdays and one weekend day) using an electronic app or by hand if the participant does not have a smart phone. EE will be assessed

using DLW, as previously done in our Sleep Study [8], during the last 2 wk of each sleep phase. At the 4-wk compliance check, participants will be asked to provide fasting blood, urine and saliva samples prior to taking a dose of DLW (2.5 g 18O, 10% atom percentage excess [APE] and 0.12 g 2H2O 99.9% APE per kg estimated body water). This will be followed by a 50 mL water rinse. Participants will be asked to minimize food and beverage consumption over the following 4 h and to collect saliva samples at 3 and 4 h post-dosage. Participants will be given vials to collect these samples as well as cups to collect second void urine samples at 24 h, 7 d, and 14 d post-dosing. Participants will be asked to freeze their samples at home and bring them to the research center at the next compliance check visit. Isotope measurements will be made by Off-Axis Integrated Cavity Output Spectroscopy in the laboratory of Dr. Edward Melanson at the University of Colorado.
Older participants enrolled in this study will undergo the same procedures as the younger participants enrolled in the parent study except for two assessments: (1) functional neuroimaging of brain responses to food stimuli and resting-state neuroimaging; (2) doubly-labeled water dosing for measurements of free-living energy expenditure. These measurements cannot be performed due to budgetary constraints and given the focus on cognitive function for this supplement. However, all other assessments, including measurements of body composition by MRI, hormone and metabolite assessments, and measurements of food intake and physical activity level, will be performed. In addition, participants in the parent cohort who will be enrolled in this study during the time of this award will undergo additional assessments related to cognitive function and imaging as detailed below. A structural brain MRI acquisition protocol to measure cortical thickness, regional volumes, and markers of cerebrovascular disease will be included for both younger and older participants.

Participants will perform tests included in the NIH Toolbox at baseline and week 6 of each study phase. The test battery will be performed in the morning, after an overnight fast, in conjunction with blood sampling.These computerized tests will be supplemented with the ModRey. For this test, participants are read a series of words and asked to recall them during three learning trials, after a brief delay, and after a longer delay. There is also a distractor list and a memory recognition trial. The learning and short delay trials will be administered prior to administration of the NIH Toolbox and the long delay and recognition trials will be administered afterwards. Psychometrically similar alternative forms are available and will be counterbalanced.

Structural brain imaging will be performed at Columbia University Irving Medical Center. This procedure will take place in conjunction with the whole-body scan that is currently performed in the parent study and will only be performed at baseline of phase 1. The protocol derives measures of brain atrophy/volumetry and white matter hyperintensities, but we will also examine microbleeds and infarcts for secondary analyses. Scanning will take place in a single session and include a high-resolution T1-weighted anatomical scan (MPRAGE), T2-weighted FLAIR, and gradient echo (GRE). We will also collect diffusion-weighted imaging and diffusion tensor imaging data for secondary or exploratory analyses. The MRI data will be transferred to a PACS for clinical review and via established, secure DICOM servers the data are also transferred to Dr. Brickman's laboratory for analysis.

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such

as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Sample size determination. We will enroll 66 participants and expect 50 to complete the study. This drop-out rate accounts for participant non-compliance. In our previous Sleep Study, our completion rate was 90%. We expect a larger drop-out rate in the proposed study due to the longer duration of each treatment phase, and we also anticipate dismissing some participants due to non-compliance. Each participant will undergo 2 study phases, and each response variable will be measured at least once per phase. Thus, for each response measure we will have at least 50 x 2 paired observations. We have analyzed preliminary data consisting of a number of measurements from 2 overweight women from our Pilot Study. Based on preliminary data analysis we have estimated an effect size (mean paired difference) of 0.69 ± 0.36 g for fat mass and an effect size (mean paired difference) of 0.91 ± 0.65 g for weight gain. This translates to very large effect sizes of 1.92 (fat mass) and 1.4 (weight gain) for paired t-tests. With these effect sizes we have more than 99% power for paired t-tests.] We have estimated the EI effect size to be 295.9 ± 116.3 kcal [8]. The effect size for a paired t-test (effect size divided by the standard deviation) for a paired t-test is >2, which is a very large effect size for paired t-test. This means with 50 x 2 paired samples, we have >80% power for paired t-test. In St-Onge et al. 2011 [8], we also reported an effect size of 20.7 ± 6.8g for fat intake and an effect size of 57.9 ± 32.6 g for carbohydrate intake. This translates to very large effect sizes of 3.04 and 1.78, respectively for fat and carbohydrates for paired t-test. With these effect sizes we have >80% power for paired t-test. Moreover, using the R2 value from our linear model analysis of St-Onge et al.2011, we determined that we have>80% power for proposed linear mixed model analyses (as described in statistical plan) with energy balance, fat and carbohydrate intakes. Thus, we have very good power overall, which will be useful in our primary analyses as well as in exploring sex differences. Statistical plan. Exploratory data analyses for physiological, anatomical, biomarker and intakerelated responses will be performed using R, SAS and other software. As part of the analysis, we will compute descriptive statistics for each variable. In particular, we will compute the proportion, mean, variance, standard error and the range of continuous variables and frequency and mode for discrete variables. Descriptive statistics will be computed for each specific sleep phase. In addition, correlation coefficients between the variables will be computed and scatter plots will be checked for linear relationships. The correlations and scatter plots help assess the degree of collinearity among variables, which will be useful for interpreting regression-based linear mixed model analyses discussed later. The data will be tested for normality, and if needed an appropriate transformation will be used on the raw data to make the normal approximation better. We will have a comprehensive strategy to deal with missing data. We will study missingness to decide if the data are missing at random or missing completely at random. Missing rates will also be estimated for each variable. Missing values will be imputed, as appropriate. We will fit a linear mixed model to analyze the data. Treatments (sleep duration: SR vs. HS) will be fixed effects and subjects a random effect. As we are collecting data from two phases for each subject, we will test for carryover effects by using a treatment x phase interaction in an initial version of each linear model. If the interaction term is not significant then we will rebuild the linear model without the interaction term. The other independent variables (covariates) will be sex, age, baseline BMI, and race/ethnicity. If required anywhere in the analysis plan, p-values will be adjusted for multiple comparisons. Sp. Aim 1: Hypothesis 1a. SR will lead to increased total adipose tissue mass, as assessed using MRI, relative to HS. We will perform repeated measure linear mixed model analyses separately for adipose tissue mass increase and weight gain (as the response). Sleep duration (SR vs. HS) and the covariates will be used as independent variables. Subject will be used as a random effect. Paired t-test and Wilcoxon test will be used to determine whether the SR and HS have different

effects on weight gain and adipose tissue mass increase.Hypothesis 1b. EE, assessed by DLW, and physical activity level, monitored daily by actigraphy, will be lower during SR relative to HS. We will perform repeated measure linear mixed model analyses separately for DLW and actigraphy-derived variables as the responses. Sleep duration (SR vs. HS) and the covariates will be used as independent variables. Subject will be used as a random effect. Paired t-test and Wilcoxon test will be used to determine whether SR and HS have different effects on DLW and actigraphy measures.Sp. Aim 2: Hypothesis 2a. EI, assessed by [3-d food records], will be greater during a period of SR relative to HS. This will be mostly due to increased fat and carbohydrate intakes. We will perform a repeated measure linear mixed model analyses separately with each EI measure (as the response) and sleep duration (SR vs. HS) and the covariates as independent variables. Subject will be used as a random effect. Paired t-test and Wilcoxon test will be used to determine whether the SR and HS have different effects on EI measures.Hypothesis 2b. Neural responses to food stimuli, assessed by fMRI after 6 wk of SR or HS, will indicate increased activity in networks associated with reward and food valuation (insula, orbitofrontal cortex) during a period of SR relative to HS. These responses will be correlated with intakes of high carbohydrate and high fat foods (hypothesis 1a) and [ghrelin]. Connectivity of the networks involved in reward valuation at rest will be stronger after SR compared to HS and synchrony of the DMN will be reduced after SR compared to HS.Sp. Aim 3: Hypothesis 3a. SR will lead to [increased glucose, insulin, triglycerides, and reduced highdensity lipoprotein cholesterol and adiponectin relative to HS.] We will perform repeated measure linear mixed model analyses separately for each of glucose, insulin, triglycerides, high-density lipoprotein cholesterol and adiponectin. Sleep duration (SR vs. HS) and the covariates will be used as independent variables. Subject will be used as a random effect. One-sided paired t-test and Wilcoxon test will also be used to determine whether the SR and HS have different effects on the cardio-metabolic risk profiles, as well as the direction of the effects. Hypothesis 3b. Increased adiposity and poor diet quality (higher fat and carbohydrates) after SR will partially explain the adverse cardio-metabolic risk profile associated with SR. We will select the cardiometabolic risk profile variables that are adversely associated with SR. Then, we will compute the difference in those variables in SR vs. HS (i.e. the value of each variable in SR minus the value of that variable in HS). Using a linear model analysis, we will test if these differences are associated with increased adiposity and poor diet quality. If, for some variables, there are multiple observed differences for each subject then a linear mixed model analysis will be used with subject as a grouping variable. A separate analysis will be performed for each such difference, with the difference as the response variables and adiposity, food quality variables and the covariates as dependent variables. *Linear Mixed Model Analyses.*We will fit a linear mixed model to analyze the data. Treatments (SR vs. HS) will be used as fixed effects and subject will be used a random effect. The other independent variables, such as demographic variables, will be covariates. Those covariates will be removed if they do not significantly contribute to the model.Aim 4: (To determine whether long-term mild SR, relative to HS, challenged acute cognitive outcomes in older and younger adults. Hypothesis 4a. Mild SR will induce cognitive decline, assessed using with the NIH Toolbox, which will be greater in older relative to younger adults.) Outcomes are measures from the NIH Toolbox. Each outcome will be analyzed in separate linear mixed model analyses, for older and young participants, as detailed in "*Linear Mixed Model Analyses"* section above. Sleep (SR vs. HS), along with phase (1 vs. 2), carryover effects, and covariates (if they are found to be significant in an initial analysis) will be used in the model. Subject will be used as a random effect. Then, we will pool the datasets to include both older and young participants. In the pooled dataset, we will use the average differences in NIH Toolbox measures (from HS to SR) as outcomes in linear model analysis. Age group (older vs. younger) will be used as main predictor variable. We will also apply covariates as independent variables, if they are found to be significant in an initial analysis. We will use unpaired t-test on the average difference in

NIH Toolbox measures (from HS to SR), to test if these values are significantly different between older and young participants.Aim 5: (To determine whether the effects of SR on cognitive outcomes are moderated by brain atrophy in younger and older adults. Hypothesis 5a. The effect of mild SR on cognition will be greater among individuals with greater amounts of cortical thinning, smaller hippocampi, and greater WMH volume. This effect will be greater in older relative to younger adults.) Separately for older and young participants, we will perform linear model analyses, with average differences in NIH Toolbox measures (from HS to SR) as outcomes (separately for each outcome). Cortical length, hippocampi size and WMH volume will be used as independent variables. We will apply covariates as independent variables, if they are found to be significant in an initial analysis. Then, we will pool the datasets to include both older and young participants. In the pooled data, we will perform linear model analyses, with average differences in NIH Toolbox measures (from HS to SR) as outcomes. Cortical length, hippocampi size, WMH volume and age group (older vs. younger) will be used as independent variables. We will also use covariates as independent variables, if they are found to be significant in an initial analysis.Aim 6: (To determine whether changes in metabolic or hormonal profiles mediate changes in cognitive function as a result of SR. Hypothesis 6a. The effect of mild SR on cognition will be mediated by changes in hormones (leptin, adiponectin, and insulin).) Separately for older and young participants, and separately for each hormone measure, each outcome (from NIH toolbox) will be analyzed with mediation analysis (Baron and Kenny's method). Sleep type (SR. vs HS) will be the predictor in the analysis. Hormone measure will be used as the potential mediator. As we have multiple measures from each participant, each component analysis in Baron and Kenny's method will be done as linear mixed model analysis, with subject as random effect. Within each mediation analysis, the first analysis will only have one fixed effect: sleep (SR vs. HS). The outcome measure will be the dependent variable. If sleep is found to be significant, then the second analysis will be done with the hormone measure as the dependent variable, and sleep as the fixed effect. If sleep is also found to be significant in the second analysis, then in the final analysis, the outcome measure will be the dependent variable. Fixed effects will be sleep and the hormone measure. If the hormone measure is still found to be significant, and the coefficient of sleep has decreased in absolute value from the first analysis, then a mediation effect of hormone will be concluded.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):
No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?
No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?
Yes

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State /Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
Federal/State/ Local Government	NIH	National Heart, Lung, and Blood Institute/NIH/ DHHS	Awarded/Received	R01HL128226	Direct Recipient: With Subcontract Sites	Entire Protocol	PT-AABL8020
	Subcontract site(s), procedures taking place at each site and FWA# for federally funded studies: NYULMC performs fMRI measurements; University of Manitoba is analyzing doubly-labeled water samples						

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Columbia/CUMC	21 Audubon Avenue, basement				
Columbia/CUMC	Neurological Institute, Basement				
Columbia/CUMC	NYP 10				
Columbia/CUMC	Russ Berrie				

Personnel

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
ms2554 212-851-5578	St Onge, Marie Pierre	Principal Investigator	MED General Medicine (751880X)	Edit	Y
amb2139 212-342-1378	Brickman, Adam	Investigator	TBI Cognitive Neuroscience (7581305)	Edit	N
	Roles and Experience: Neuroimaging and neuro-cognitive testing				
as4874 917-968-3208	Shechter, Ari	Investigator	MED Behavioral Cardiology (751890X)	Edit	Y
bbl14 212-851-5562	Laferrere, Blandine	Other Engaged Personnel	MED Obesity (752060X)	View	N
	Roles and Experience: medical supervision				
bc2159 212-342-1238	Cheng, Bin	Investigator	BST Biostatistics (821000X)	View	N
	Roles and Experience: statistical analyses				
cwb11 212-305-1742	Bazil, Carl	Investigator	NEU Epilepsy Operations (7524502)	View	N
fmz2105 724-549-7905	Zuraikat, Faris	Other Engaged Personnel	MED General Medicine (751880X)	Edit	Y
	Roles and Experience: Post-Doctoral Fellow; expertise in data analyses				

UNI/Phone	Name	Role	Department	Edit/View	Obtaining Informed Consent
gb2710 845-548-3569	Benasi, Giada	Other Engaged Personnel	MED General Medicine (751880X)	Edit	N
	Roles and Experience: New post-doctoral fellow				
kci2104 281-300-6376	Igwe, Kay	Other Engaged Personnel	ENG PROF CHRISTOPH JUCHEM LAB (5218209)	View	N
	Roles and Experience: Neuroimaging and neuro-cognitive testing				
mep2238 520-909-1711	Petrov, Megan	Other Engaged Personnel	MED General Medicine (751880X)	View	N
	Roles and Experience: sleep and health, data analysis				
ws2003 212-851-5572	Shen, Wei	Investigator	PED Gastroenterology (754110X)	View	N

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	GCP - Third-party tracking	GCP Refresher	Genetic Research Consent
ms2554	St Onge, Marie Pierre	04/10/2023	12/20/2013	04/06/2022	06/18/2019	06/18/2019					09/09/2022	
amb2139	Brickman, Adam	04/07/2023	12/02/2004	12/28/2022	12/28/2019	12/21/2012	12/21/2012				11/28/2022	
as4874	Shechter, Ari	05/24/2023	10/27/2011	06/26/2023	07/25/2011	09/23/2020					08/02/2022	
bbl14	Laferrere, Blandine	01/04/2024	07/16/2020	12/08/2022	06/16/2017	06/23/2014	09/29/2014				01/31/2023	
bc2159	Cheng, Bin	01/12/2024	10/20/2004	01/11/2023	01/11/2023	01/11/2023					05/15/2022	
cwb11	Bazil, Carl	01/17/2024	07/09/2004	09/06/2022	09/29/2006	02/03/2017					09/06/2022	
fmz2105	Zuraikat, Faris	01/16/2024	09/07/2018	10/16/2021	09/07/2018	03/19/2020			03/15/2023		03/15/2023	10/25/2021
gb2710	Benasi, Giada	06/09/2023	01/05/2020	10/05/2022	07/20/2021	07/20/2021			10/06/2022		10/05/2022	10/25/2021
kci2104	Igwe, Kay	11/13/2023	02/26/2015	01/13/2023	03/03/2021	03/03/2021						
mep2238	Petrov, Megan	06/02/2023	01/12/2024	12/19/2023		11/29/2023			12/21/2023			
ws2003	Shen, Wei	11/15/2023	04/17/2014	05/20/2021	05/19/2021	08/13/2018					12/29/2022	

Departmental Approvers

Electronic Signature:	Megan Petrov (751880X) - Other Engaged Personnel	Date: 12/11/2023
Electronic Signature:	Bin Cheng (821000X) - Investigator	Date: 01/08/2024
Electronic Signature:	Marie Pierre St Onge (751880X) - Principal Investigator	Date: 01/16/2024

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[x]Hardcopy (i.e., paper)

Describe where and how the data will be stored:

All files with participant identifying information will be kept in a locked file cabinet in the PI's office

[x]Electronic

Where will the data be stored?

Y

[x]On a System

[x]On an Endpoint

Identify what type of endpoint will be used (select all that apply):

[x]Desktop Computer

[x]Laptop Computer

[ ]Mobile Device

[ ]Other

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

[x]Personally Identifiable Information (PII), including Social Security Numbers (SSN)

Will Social Security Numbers (SSNs) be collected for any purpose?

Yes

Describe the purpose for collection of SSNs:

subject payment

Describe the plan to protect SSN confidentiality:

w-9 forms will not be stored with subject data

Will SSNs be disclosed outside of Columbia for any purpose?

No

[x]Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

[ ]Sensitive data will not be stored in electronic format

[ ]Sensitive data will be stored on a multi-user system

[x]Sensitive data will be stored on an encrypted endpoint

By Selecting an Endpoint Device and approving this protocol for submission to the IRB, the PI is attesting that the device and any removable media that may be used have been or will be registered and/or will be maintained in compliance with the University's Information Security Charter and all related policies. It is important that this information is updated, during the course of the study, as new devices are added.

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

Data files will be password protected and exchanged in secured servers. Only individuals involed in the study conduct will have access to those files and HIPAA regulations will be followed. All data transmitted among investigators will be coded and shared via encrypted devices. Data obtained via mobile devices (e.g., tablets) will not contain PII/PHI, and will be transferred to secure endpoints via the CUMC athens wireless network, or otherwise via a physical connection (e.g. USB, microSD).

If your project is not NIH funded, has a Certificate of Confidentiality (CoC) been requested for this research?

No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:

Data files will be password protected and exchanged in secured servers. Only individuals involed in the study conduct will have access to those files and HIPAA regulations will be followed. All data transmitted among investigators will be coded and shared via encrypted devices. Data obtained via mobile devices (e.g., tablets) will not contain PII/PHI, and will be transferred to secure endpoints via the CUMC athens wireless network, or otherwise via a physical connection (e.g. USB, microSD).

Procedures

Is this project a clinical trial?

Yes

Is this project a clinical trial that requires registration with www.clinicaltrials.gov?

Yes

Has this study been registered with www.clinicaltrials.gov?

Yes

Please provide the registration number:

NCT02960776

Is this project associated with, or an extension of, an existing Rascal protocol?

No

Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review

No

Audio, video or photographic recording of research subjects

No

Behavioral Intervention?

Yes

Biological specimens (collection or use of)

Yes

Cancer-related research

No

Drugs or Biologics

No

Future use of data and/or specimens

Yes

Genetic research

No

Home Visits

No

Human Embryonic and/or Human Pluripotent Stem Cells

No

Imaging procedures or radiation

Yes

Medical Devices

Yes

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

Yes

NOTE: You must attach a PDF version of the survey(s)/interview(s)/questionnaire(s) to this protocol prior to submission.

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

Yes

Educational testing

No

Non-invasive physical measurements

Yes

Taste testing

No

Is there a stand-alone protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

Overview of Procedures

We propose a randomized, crossover, outpatient sleep restriction study with 2 phases of 6 wk each. The sleep durations will be the participant's regular bed- and wake-times during the HS phase and HS minus 1.5 h in the SR

phase. During the HS phase, participants will be asked to follow a fixed bedtime routine based on their screening sleep schedule. During the SR phase, participants will be asked to keep their habitual wake time constant but delay their bedtime to achieve a reduction of 1.5 h in total sleep time. A delay in bedtimes was chosen rather than advancing wakeup time because it most closely reflects differences in sleep timing behavior between short and habitual sleepers. In fact, the longer sleep duration of individuals in the Central time zone compared to that of those in Eastern or Pacific time zones [58] is hypothesized in part to be due to late night shows being broadcast one hour earlier in the Central time zone [59]. Individuals in Eastern or Pacific time zones stay up later at night to watch those shows. Adolescent short sleepers have later bedtimes than normal sleepers [60]. Moreover, delaying bedtimes increases exposure to light at night which is associated with weight gain and obesity [61]. Providing individualized bedtimes and wakeup times for each participant was chosen to ensure that participants are not phase-shifting their sleep episode for the purpose of this study. Two weeks prior to randomization and during washout periods, participants will wear an actigraph (ActiGraph wGT3X-BT activity monitor, Pensacola, FL) and keep a sleep diary to verify sleep duration and sleep-wake schedule. In addition to achieving an average sleep of 7-9 h/night, per wrist actigraphy, participants will only be enrolled if they achieve 7 h of sleep for at least 10 of the 14 nights of screening and have <4 nights with <6 h of sleep. We have successfully used this screening protocol in several studies [8, 28]. The actigraph monitors will be provided by the research team. At randomization, a urine pregnancy test (for women) and drug screen will be performed. Participants will be asked to abstain from caffeine and alcohol intake for 24 h prior to the start of each study phase. Between study phases, if participants have not returned to baseline sleep patterns, an additional 2-4 wk washout period will be provided. In general, washout periods will be 6 wk in duration. This washout length enhances the likelihood that women will be in the same phase of their menstrual cycle at the start of each experimental phase
On the first day of each study phase (baseline), participants will come to Irving Center for Clinical and Translational Research (CTSA) at Columbia University in the morning after an overnight, 12-h fast. Participants will have anthropometric and blood pressure measurements taken, will provide a fasting blood sample, undergo performance/vigilance testing, and will then be taken to the department of Radiology to undergo MRI scanning to assess body composition. Participants will begin the fixed bedtime routine that night. These baseline measurements will be repeated at endpoint, 6 wk later. Body weight, waist circumference, and blood pressure will be measured weekly, fasting blood and urine samples will be taken at baseline, week-3, week-4, and endpoint, during adherence check visits. A non-fasting blood sample will be taken at week-5 adherence check visits. During the last week of each phase, 1 h before the participant's self-reported usual dinner time they will be escorted to NYU for an fMRI. They will fill out a visual analog scale and the Stanford Sleepiness Scale, before and after the scan. During the last week of each phase, participants will undergo performance testing (6-minute walking test).

Ensuring adherence to the sleep protocol.
Participants will be blinded to the purpose of the study to ensure that they do not alter their habits by knowing the hypothesis that SR may cause weight gain. Participants will be told that the purpose of the study is to assess the effects of mild SR on mood and cognitive and physical performance. Questionnaires and physical performance tests will be administered at baseline and bi-weekly, to maintain blinding. We also have a well-defined strategy for ensuring adherence to the sleep protocol in this outpatient setting. Participants will be given written instructions on study procedures and investigator phone calls will be made as reminders of the bedtimes and wakeup times on a weekly basis. To verify that participants adhere to the sleep protocol, they will be asked to keep a sleep diary and wear an activity monitor 24 h/d. Participants will wear an actigraphy monitor on their wrist (ActiGraph wGT3X-BT activity monitor, Pensacola, FL), which will serve to track their sleep duration, sleep timing, and ambient light. This watch is water resistant and therefore does not need to be removed to shower or swim. To further ensure compliance with the sleep protocol, participants will be required to come to the research center on a weekly basis. This weekly visit will serve several purposes: (1) download data from the Actiwatch (verify sleep duration); (2) charge the watch; (3) obtain weekly diaries (verify bedtimes and wakeup times) and other questionnaires; (4) obtain body weight measurement and blood and urine samples. Participants will be told a priori, as part of the screening process, that they must adhere to the sleep protocol to continue to participate in the study and that adherence will be checked weekly. Non-adherent

participants will be terminated from the study. Adherence will be defined as having bedtimes and wake times within 30 min of scheduled times at least 5 d/wk and achieving an average of >7 h of sleep each week with no more than one night/wk of sleep <7 h during the HS phase and achieving an average sleep reduction of 1.5 h from screening sleep duration each week with no more than one night/wk with <1.5 h of restriction during the SR phase. Daytime naps will not be permitted. Participants will receive weekly incentives, in the form of a gift card, for their continued adherence to the sleep protocol.

Detailed methods for outcome variables

Body composition measurements.
Anthropometric measurements will be obtained at the NYORC Human Phenotyping/Body Composition Core Laboratory (Dympna Gallagher, Ed.D. Core laboratory Director). A single trained technician will obtain all measurements for this study using laboratory standard procedures. Height, weight, and body circumferences (waist and hip) will be measured in duplicate with the participant wearing only a hospital gown and no shoes. The Body Composition Laboratory is a world-renowned center for the measurement of body composition and has been involved in cutting-edge research for the development of new body composition assessment techniques, estimation equations, and validation of new measurement tools.

Body composition will be measured by MRI at baseline and endpoint. Briefly, a full body scan will be done using a 1.5T GE MRI (GE Healthcare) in the Department of Radiology at Columbia University Medical Center. We acquire 10 mm thick slices at 40 mm intervals throughout the body. All body compartments will be segmented at the New York Image Analysis Laboratory (Wei Shen, MD, Core laboratory Director) by trained technicians, who regularly undergo quality control and cross-validation, using SliceOmatic image analysis software (Tomovision, Montreal, Canada). Technicians will be blinded to sleep study phase assignment and test dates. This protocol will allow us to quantify muscle mass, organ mass, and subcutaneous, visceral, and intermuscular adipose tissues for the whole body and for left and right sides and upper and lower body. MRI provides images of the entire visceral area, a major advantage over other imaging techniques. Another advantage of this methodology is the lack of radiation exposure and whole-body measurements of visceral and subcutaneous adipose tissues. As MRI scanning is very safe, repeated measurements can be performed frequently on the same individual. In this study, we chose to perform a whole-body scan rather than the common single-slice imaging as we have shown that multi-slice imaging was better and more cost-effective at detecting changes in visceral and subcutaneous adipose tissue than a single slice. In the present study, participant costs are higher than imaging costs. Therefore choosing a more precise body composition assessment method that reduces the need for additional participants represents a cost-saving option.

Energy expenditure.
EE will be assessed using doubly labeled water (DLW), during the last 2 wk of each sleep phase. At the 4-wk compliance check, participants will be asked to provide a urine and a saliva sample prior to taking a dose of DLW (1.6 - 2.5 g 18O, 10% atom percentage excess [APE] and 0.12 g 2H2O 99.9% APE per kg estimated body water). This will be followed by a 50 mL water rinse. Participants will be asked to minimize food and beverage consumption over the following 4 h and to collect saliva samples at 3 and 4 h post-dosage. Participants will be given vials to collect these samples as well as cups to collect second void urine samples at 24 h, 7 d, and 14 d post-dosing. Participants will be asked to freeze their samples at home and bring them to the research center at the next compliance check visit. Isotope measurements will be made by Off-Axis Integrated Cavity Output Spectroscopy in the laboratory of Dr. Edward Melanson (Anschutz Medical Campus, University of Colorado, CO). These measurements will be obtained in younger adults only.
We will also assess physical activity level by waist actigraphy (GT3X Actigraph LLC, Pensacola, FL) throughout each study phase. We hypothesize that total EE and physical activity level will be lower during the period of SR compared to

HS.

Resting-state and food-viewing stimulated neural activity.
Brain responses will be assessed using two fMRI paradigms (resting state and task-based) at wk 6, 1 h before the participant's self-reported usual dinner time. The resting state paradigm and intrinsic functional connectivity (iFC) analysis will assess treatment effects on reward and interoception-related neuronal circuitry. During the resting state scan (2 runs, each ~ 5 mins), participants will focus on the fixation cross in the center of the screen. Wakefulness and compliance with eyes-open instructions will be monitored via an eye-tracking camera and verbal reminders given before every run. Pulse and respiration rates will be measured using MRIcompatible non-invasive physiological monitoring equipment. Recent data by Fang et al. [71] reported altered resting state striatal connectivity after a night of total sleep deprivation, which was correlated with increases in EI. We will explore whether this is the case in the proposed conditions. The task-based paradigm has been validated in several studies, including our Sleep Study. The 2-by-2 block design protocol includes 4 runs (~3 min each) each consisting of 4 blocks (2 foods and 2 non-foods) during which participants view 5 items presented for 4 s each (total=20 s) using E-Prime 2 (Psychology Software Tools, Inc., Pittsburgh, PA). Each block is separated by a 20 s basal period during which participants view a fixation cross. [The order of blocks in a run is constant for each participant with the specific stimuli that the individual ranked highest in a preference rating questionnaire prior to scanning. Our pilot R56 grant data (R56 HL119945) suggested a relatively uniformly distributed range of preferences across the initial 40 food and 40 non-food items that each participant ranked. This preliminary finding supports the feasibility of including images that are rated as "mildly appealing" up to "very appealing".] Importantly, in our previous Sleep Study, scanning was performed in the fasted state in the morning. Since it has been proposed that SR induces greater evening intakes specifically, we chose to perform our measurement approximately 1 h prior to the participant's usual dinner, a time when individuals may be most susceptible to be hyper-responsive to food stimuli in SR relative to HS, thus increasing sensitivity for capturing the effect of SR.

Imaging parameters.
fMRI scanning will take place at the NYULMC Center for Biomedical Imaging using [the same Siemens 3T Skyra scanner (Siemens USA, Malvern, PA) used in our R56 pilot study.] Head motion will be minimized by placing restraint pads around the head. A T1-weighted anatomical image [(MPRAGE sequence: TR=1900 ms; TE=2.52 ms; TI=900 ms; flip angle=9°; 176 slices, FOV=250 mm, voxel size=1x1x1 mm) will be acquired for image co-registration and spatial localization. For both resting-state and task-based paradigms, functional data will be acquired using a single-shot gradient echo planar imaging (EPI) T2*-weighted sequence (TR=2500 ms; TE=30 ms; Flip angle=80°, 38 slices, matrix=64x64; FOV=216 mm; voxel size=3x3x3 mm).] To examine structural connectivity, we will acquire diffusion-weighted data using an echo-planar sequence (TR=5.2 s, TE=78 ms, 32 directions, b=1000 s/mm2; acquisition voxel size=2x2x2 mm).

Image analysis.
Image processing will be carried out using [FMRIB Software Library (FSL, www.fmrib.ox.ac.uk) and Configurable Pipeline for the Analysis of Connectomes (C-PAC, http://fcpindi.github.com).] Preprocessing will comprise (1) slice time correction, (2) 3-D motion correction, (3) spatial smoothing (FWHM=6 mm), (4) mean-based intensity normalization, (5) temporal band-pass filtering (restingstate data only; 0.009-0.1 Hz), and (6) linear and quadratic detrending. Linear registration of each participant's functional time series to their high-resolution structural image and non-linear registration of high-resolution structural images to the Montreal Neurological Institute (MNI) template with 2 mm resolution will be performed using FLIRT and FNIRT [73, 74]. [Given that head motion in 100% of our preliminary task-related and resting state data was much lower than field standards (mean head motion for each of the 4 task and 2 rest functional runs ranging between 0.073 mm and 0.078 mm, substantially lower than the field standard of 0.2 mm), we anticipate implementing 'scrubbing' to salvage offending segments with excessive motion, if necessary. Task:

Neural responses during food and non-food blocks will be assessed using a box-car convolved with a hemodynamic response function (HRF) as implemented in FEAT [78]. A direct contrast of food relative to non-food blocks will identify brain regions sensitive to food processing. Group-level random-effects analyses will compare neural activation for food>nonfood stimuli using paired t-test between HS and SR. Whole-brain correction for multiple comparisons will be performed ($Z>2.3$; cluster significance: $p<0.05$, corrected). Finally, we will use resting state and task-based data to assess activity of the DMN (regions of the posterior cingulate gyrus, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and hippocampus).

Resting-state and food-viewing stimulated neural activity will be measured in younger adults only.

Appetite & food intake measurements.

Throughout the study, participants will self-select their food intake in a freeliving situation. Food intake will be assessed at baseline, wk 3, and wk 6 by 3-d food records (2 weekdays and one weekend day) using a free electronic app, such as MyFoodCircle, HealthWatch 360, or other similar app; or on paper. Participants could be asked to provide pictures of their food to assist in data collection. In the proposed study, we are interested in qualitative assessment of diet and comparison of intakes between phases. Nonetheless, quantitative assessments will also be available. Since participants will be blind to the true objective of our study, we do not expect reporting error to systematically vary based on study phase and can have confidence in our measurement tool. The within-subject study design is essential in this regard. Moreover, the true assessment of energy balance is change in body composition: weight gain invariably signifies positive energy balance whereas weight loss represents negative energy balance. Energy and macronutrient intakes will be assessed using the University of Minnesota Nutrition Data System for Research (NDSR, Minneapolis, MN).

Assessment of metabolic parameters.

Fasting blood samples will be taken at baseline, wk 3, wk 4, and endpoint of each sleep phase for measuring lipid profile, glucose, insulin, adiponectin, leptin, ghrelin, and GLP-1. [92]. All samples will be analyzed in the Hormone and Metabolite Core laboratory of the NYORC (Dr. F. Xavier Pi-Sunyer, Core laboratory Director) by skilled technicians. Insulin will be assayed using a radioimmunoassay (RIA; Linco Research Products Inc., St. Charles, MO; mean inter-assay CV 4.5% [93, 94]). Serum leptin will be measured using a double-antibody RIA (Linco Research; inter-assay CV 6.8% [93, 94]). Cortisol will be assay using enzyme immunoassay (DPC, Los Angeles, CA). 6-Sulfatoxymelatonin will be assayed from morning urine samples as a proxy for overnight melatonin production [95] using ELISA kit (ALPCO, Salem, NC). Blood samples will be collected in EDTA-coated chilled tubes for measuring peptide hormones. The tubes will be pre-treated with addition of aprotinin (0.6 TIU/mL of blood) and DPP-IV inhibitor (10 L/mL of blood) to prevent hormone degradation. Total ghrelin will be assessed using RIA (Linco Research; inter-assay CV 6.3% [96]). Adiponectin levels will be analyzed using RIA (Linco Research). GLP-1 will be assessed using RIA (Phoenix Pharmaceutical, Belmont, CA). An additional blood sample will be collected in silica-coated serum separating tubes to measure thyroid stimulating hormone, free T4, and sex hormones (testosterone, estrogen, progesterone, FSH, and LH).

Questionnaires.

In addition to the screening questionnaires, several questionnaire will be administered at baseline and endpoint of each phase.

1) The SF-36v2 health questionnaire will provide an objective measure of quality of life over the course of each phase.

2) Similarly, the Montreal Cognitive Assessment (MOCA), the NIH Toolbox, and the ModRey will be administered at baseline and endpoint of each phase to evaluate general cognitive function. Any findings of cognitive impairment will be disclosed to the research participant.

3) Although the caffeine consumption questionnaire is initially administered as a screening tool (must consume <300 mg/day), we will also administer it at baseline and endpoint of each phase to assess changes in caffeine consumption.

4) Perceived Stress Scale 10-item and the Hospital Anxiety Depression Scale-Anxiety sub scale will be administered at baseline, wk 3, and 6 of each phase.

Performance tests.
During the last week of each study phase, preferably on the 5th follow-up visit (the 7-d visit after DLW dosing), participants will undergo a 6-min walking test. This test will be administered in the CRR on a 30-m walking course. Participants will be instructed to walk as fast as possible to cover the most distance over a 6-min period. The research assistant will provide information on time remaining at each minute.
The psychomotor vigilance test (PVT) will be administered at baseline, week 3, and week 6, using an app on an Android tablet. This test will be done at the time of the blood sampling procedure.

Structural brain imaging.
Structural brain imaging MRI protocol. MRI scanning will take place on a 3T Philips Achieva scanner located at Columbia University Irving Medical Center. This procedure will take place in conjunction with the whole-body scan that is currently performed in the parent study and will only be performed at baseline of phase 1. The protocol derives measures of brain atrophy/volumetry and WMH, but we will also examine microbleeds and infarcts for secondary analyses. Table 1 displays the pulse sequences collected for this study. Scanning takes place in a single session and includes a high-resolution T1-weighted anatomical scan (MPRAGE), T2-weighted FLAIR, and gradient echo (GRE). We also collect diffusion-weighted imaging and diffusion tensor imaging data for secondary or exploratory analyses. The MRI data will be transferred to a PACS for clinical review and via established, secure DICOM servers the data are also transferred to Dr. Brickman's laboratory for analysis.

Global and regional atrophy. Using each individual's T1-weighted image, structural imaging measures of both global and regional brain volume and measures of cortical thickness are derived with FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Primary volumetric measures will be hippocampal, entorhinal cortex, and total brain volume. We will also assess cortical thickness as specific patterns of cortical thinning found in Alzheimer's disease [20, 46]. Again using Freesurfer software [47, 48], we will calculate mean thickness in 33 different gyral-based areas in each hemisphere [49]. The primary cortical thickness measure [20, 46] will include the average thickness in Alzheimer's disease -related regions [50]. Volumetric and cortical thickness in all regions are databased for secondary analyses.

Microbleeds. Microbleeds are rated by visual inspection following criteria put forth by Greenberg et al. [51-53]. The primary measure is the presence or absence of lobar microbleeds, indicating possible or probable cerebral amyloid angiopathy [54]. The number of microbleeds and location are coded and databased for each participant.
Infarct. All available MRI data are used to define radiological infarcts. Infarcts are rated as discrete hypointense lesions that are larger than 5mm surrounded by a complete hyperintense ring on FLAIR. The primary measure is presence or absence of infarct, but several summary measures are generated, including number, size, and location.

Biological Specimens

Add an individual entry for each human specimen type that will be collected or utilized for the proposed study. For each specimen type, indicate the source or sources from which you will obtain the specimens.

The use of specimens for research purposes may require that informed consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) be obtained from subjects.

Type:
Saliva
Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia
Select all that apply to this specimen type:
[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia
Description of Specimen and Method of Obtaining:
Participants will be given instructions and vials to collect urine samples at home and bring to research center at their following visit.
Indicate the manner in which the specimens will be labeled:
[ ] Specimens will be labeled with direct identifiers
[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:
Blood
Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia
Select all that apply to this specimen type:
[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia
Description of Specimen and Method of Obtaining:
Blood samples by venipuncture
Indicate the manner in which the specimens will be labeled:
[ ] Specimens will be labeled with direct identifiers
[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current

researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Type:
Urine
Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia
Select all that apply to this specimen type:
[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia
Description of Specimen and Method of Obtaining:
Participants will be given instructions and cups to collect urine samples at home and bring to research center at their following visit.
Indicate the manner in which the specimens will be labeled:
[ ] Specimens will be labeled with direct identifiers
[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Devices

On the General Information page you have indicated that the protocol version associated with the use of this medical device is as follows: Y1M1-Adm Suppl

Please note that a Protocol Version # is required for protocols using a medical device, and you will not be allowed to submit this protocol until the Protocol Version # field is complete. Please ensure that the Protocol Version # is completely and accurately reported on the General Information page.

Please enter the requested information for each device that is the object of the study or is being used because it is relevant to the aims of the protocol, whether the medical device is not yet FDA-approved [i.e., is investigational] or is an approved device that is being used in an investigational manner (i.e., off-label use is being studied).

Note that the questions apply only to devices used in clinical investigations or protocols that involve a Humanitarian Use Device. Emergency use of a device that is not yet FDA-approved is not a clinical investigation,

and a submission in Rascal may not be required. Please contact the IRB for assistance if emergency use of a device that is not yet FDA-approved is being considered: (212)305-5883.

Device name:
Actigraphy monitor
Device description:
Activity monitor worn on wrist to track sleep duration, sleep timing, and physical activity
Device Model/Version #:
wGT3X-BT
Phase of Study:
Pivotal
Manufacturer Information

Name:	Actigraph Corp
Address:	49 East Chase Street. Pensacola, FL 32502
Contact information:	850.332.7900

Is the device a Humanitarian Use Device (HUD)?
No
Is the device FDA-approved and used in accordance with its labeling?
Yes
An Investigational Device Exemption (IDE) is not required. A copy of the instructions for use must be attached in Rascal.
Will a representative of the Sponsor/Manufacturer be involved with the use of the device at Columbia/ NYPH, e.g., for training purposes?
No

Future Use

For what materials do you anticipate future research use? Select all that apply.
[x]Data
[x]Biological Specimens
Please indicate how data and/or specimens will be retained for future use:
[x]Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.
How are the materials intended to be used for research in the future?
Multiple researchers, which may include the current PI and research team, will be able to request use of the materials.
What is the intent for use of the materials? (Select all that apply.)
[ ]The intent is to add the materials to an existing CU repository (e.g., HICCC Tumor Bank).
[x]The intent is to create a repository.
Does this protocol describe the repository procedures?
No, the Columbia repository protocol has not yet been created
The repository protocol should be reviewed and approved by the IRB before material is collected and ready to be entered into the repository
How will the data and/or specimens, as applicable, be labeled during storage for future uses.
[x]In the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous)
[ ]In a different manner than during collection. Select all that apply:

Describe the physical storage for the specimens/data, including location.

[x]In the same manner as during collection

[ ]In a different manner than during collection

Describe who will have access to the stored data and/or specimens.

Investigators directly involved with the study and outside investigators upon request and agreement with investigators.

[x]Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Indicate to whom the data/specimens will be released

[ ]Sponsor

[ ]Non-Columbia repository

[x]Other

Describe

Dr. Edward Melanson at University of Colorado

Describe plans for release of data and/or specimens.

Specimens will be sent to Dr. Edward Melanson at the University of Colorado to be analyzed. All specimens will labeled in the same manner as during collection. (e.g., with direct identifiers, coded, de-identified, anonymous)

Imaging Procedures/Radiation Therapy

Will a contrast agent (e.g. gadolinium) be used in conjunction with radiation exposure that goes beyond the parameters established for the applicable standard of care (SOC), or will a contrast agent be administered for research purposes only? The appropriate response would be 'no' if radiation exposure and use of contrast are solely for SOC.

No

For each type of radiation exposure (e.g., ionizing: CT, X-ray; non-ionizing: MRI), identify the procedure and whether the administration (e.g., radiation dosage, number or type of scans) is clinically indicated and in accordance with the parameters established for the applicable standard of care (SOC), or is "beyond" these parameters (i.e., includes procedures or exposure for research purposes only).

Procedure(s) Involving Ionizing Radiation

No data to display

Procedure(s) Involving Non-Ionizing Radiation

Procedure	The exposure to:	Location:
MRI	Beyond that established for the applicable SOC	

Procedure	The exposure to:	Location:
	1. Will healthy pregnant subjects be enrolled and undergo MR scanning procedures? No 2. Will healthy minor subjects be enrolled and undergo MR scanning procedures? No 3. Will new or custom (i.e., non-FDA approved) imaging equipment be used? No 4. Will non-manufacturer provided pulse sequences be used that exceed the 'Normal Mode' or, for scanning of healthy subjects, the scanner '1st Level Control Mode'? No	
fMRI	Beyond that established for the applicable SOC	
	1. Will healthy pregnant subjects be enrolled and undergo MR scanning procedures? No 2. Will healthy minor subjects be enrolled and undergo MR scanning procedures? No 3. Will new or custom (i.e., non-FDA approved) imaging equipment be used? No 4. Will non-manufacturer provided pulse sequences be used that exceed the 'Normal Mode' or, for scanning of healthy subjects, the scanner '1st Level Control Mode'? No	

Recruitment And Consent

Recruitment:

Will you obtain information or biospecimens for purposes of screening or determining eligibility?

No

Describe how participants will be recruited:

Potential participants will be recruited through local advertising media: flyers and posters in New York City, principally Manhattan, where the study will be located. These will be posted in public spaces. We will also post flyers in and around the hospitals of Columbia University Medical Center, and online on craigslist. NYPH and CUMC employees are not excluded and can be enrolled if they respond to advertisement for the study. However, they are not targeted, and will be evaluated against the same criteria as the general population. We will follow identical practices to ensure the absence of coercion into the study: participants will be told that participation in the study is completely voluntary and that they can withdraw at any time without any penalty or prejudice and will not jeopardize their care at the hospital.

Select all methods by which participants will be recruited:

[ ] Study does not involve recruitment procedures
[x] Person to Person
[ ] Radio
[ ] Newspapers
[ ] Direct Mail
[x] Website
URL: www.craigslist.org, www.studykik.com
[x] Email
[ ] Television
[ ] Telephone

[x] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[x] ResearchMatch
[x] CUMC RecruitMe

Additional Study Information: Please add a description of your study as you would like it to be displayed on the RecruitMe website.

We are currently looking for healthy, non-smoking, men and women (age 20-40 OR age 55-75 years) to participate in an at-home sleep study.

You must be willing to come to the research center once a week during the entire duration of the study (two separate 6-week periods). To participate you must regularly sleep 7-9 hours/night.

Compensation up to $2000-$2400, based on time-commitment and types of procedures, will be provided.

To see if you may be eligible, and for more information, please email Mehreen Bhatti, at mzb2107@cumc.columbia.edu

Thank you.

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[x] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:
The study in its entirety

Documentation of participation will be obtained from::
[x] Adult participants
[ ] Parent/Guardian providing permission for a child's involvement
[ ] Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:
The Coordinator specifically trained in the screening procedures and who has undergone biomedical research ethics training will be responsible for obtaining informed consent of each participant. Informed consent will be obtained as a Consent Form requiring a signature. The Coordinator will explain all of the details of the study, answer any questions that arise, and go over the scheduling and planning of the procedures. The consenting process will explain the reason for the study, all of the experimental procedures, the duration of the study, the collection and use of specimens, risks and benefits to the participant, compensation, confidentiality, and the voluntary nature of the study to the participant. The participant will be informed that they can interrupt the Coordinator at any time to ask questions, and will be asked specifically at the conclusion of the consenting procedures if they have any remaining questions on the experiment. The name, address, and phone number of the PI responsible for the study

will be provided to the participant, and they will be able to contact the PI at any time throughout the trial to ask any questions or address any issues that arise. Once interested individuals respond the posted advertisements, they will be contacted by the Coordinator in charge of this study. A consent form meeting will be scheduled at the offices where the research will be conducted (Columbia University Medical Center). No screening measurements or experimental procedures will commence until the participant provides informed consent. The duration of the consent form meeting will be roughly 1 hour. The participant will have as much time as they require for decision making, and will be allowed to discuss their choice of enrollment in the study with others before deciding to sign the consent form. Individuals will be free to not take part in the study, or to discontinue their participation in the study at any time during the study.

[ ] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

[ ] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[ ] This is exempt research.

Subject Language

Enrollment of non-English speaking subjects is not expected.

During the course of the study, if non-English speaking subjects are encountered, refer to the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details (http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc

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Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

No

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

Aim 1: Does Longer, milder SR, as observed in individuals with SSD lead to positive energy balance?Hypothesis 1a: SR will lead to increased total adipose tissue mass, as assessed using MRI, relative to HS. We will perform repeated measure linear mixed model analyses separately for adipose tissue mass increase and weight gain (as the response).Hypothesis 1b: EE, assessed by doubly labeled water, and physical activity level, monitored daily by actigraphy, will be lower during SR relative to HS.Aim 2: Is the increased EI observed in acute SR studies maintained over time?Hypothesis 2a: EI, assessed by 3-d food records, will be greater during a period of SR relative to HS. This will be mostly due to increased fat and carbohydrate intakes.Hypothesis 2b: Neural responses to food stimuli, assessed by fMRI after 6 wk of SR or HS, will indicate increased

activity in networks associated with reward and food valuation (insula, orbitofrontal cortex) during a period of SR relative to HS. These responses will be correlated with intakes of high carbohydrate and high fat foods (hypothesis 1a) and ghrelin. Connectivity of the networks involved in reward valuation at rest will be stronger after SR compared to HS and synchrony of the DMN will be reduced after SR compared to HS.Aim 3: Does Longer, milder SR, as observed in individuals with SSD adverse cardiometabolic risk profile?Hypothesis 3a: SR will lead to increased glucose, insulin, triglycerides, and reduced high density lipoprotein cholesterol and adiponectin relative to HS.Hypothesis 3b: Increased adiposity and poor diet quality (higher fat and carbohydrates) after SR will partially explain the adverse cardio-metabolic risk profile associated with SR. **Aim 4.** To determine whether long-term mild SR, relative to HS, challenges acute cognitive outcomes in older and younger adults.*Hypothesis 4a.*Mild SR will induce cognitive decline, assessed with the NIH Toolbox, which will be greater in older relative to younger adults.**Aim 5.** To determine whether the effects of SR on cognitive outcomes are moderated by brain atrophy and small vessel cerebrovascular disease in younger and older adults.*Hypothesis 5a.*The effect of mild SR on cognition will be greater among individuals with greater amounts of cortical thinning, smaller hippocampi, and greater WMH volume. This effect will be larger in older relative to younger adults. **Aim 6.** To determine whether changes in metabolic or hormonal profiles mediate changes in cognitive function as a result of SR.*Hypothesis 6a.*The effect of mild SR on cognition will be mediated by changes in hormones (leptin, adiponectin, and insulin).

Scientific Abstract:

Chronic sleep restriction (SR) is highly prevalent in today's modern society and severe sleep deprivation (SD) has been linked to obesity. We our interested in establishing whether sleep could be a causal factor in the etiology of obesity. In a recent meta-analysis, authors concluded that no studies exist to assess the effects of long-term manipulation of sleep duration on obesity risk, and proposed additional research using more standardized methods and measures, as well as evaluations of associated outcomes with sufficient sample sizes to inspect this relationship. We propose a randomized, crossover, outpatient sleep restriction study with 2 phases of 6 wk each. Sixty-six men and pre-menopausal women, age 20-40 y, BMI 20-34.9 kg/m2 (with parent with BMI >27 kg/m2 if participant BMI is 20-24.9 kg/m2), normal sleepers, free of any current and past sleep and psychiatric disorders, diabetes or CVD will be recruited. During the habitual sleep (HS) phase, participants will be asked to follow a fixed bedtime routine based on their screening sleep schedule. During the SR phase, participants will be asked to keep their habitual wake time constant but delay their bedtime to achieve a reduction of 1.5 h in total sleep time. Subjects will have anthropometric measurements taken, will provide a fasting blood sample to examine cardiovascular risk factors, and will then have body composition assessed at baseline and endpoint using magnetic resonance imaging (MRI). Body weight and waist circumference will be measured weekly, fasting blood and urine samples will be taken at baseline, week-3, week-4, and endpoint, during adherence check visits. Doubly labeled water (DLW) will be given at week 4 of each study phase will assess free-living energy expenditure (EE) and the continuous wear of actigraph monitors will provide detailed information on physical activity levels as well as monitor sleep duration. At week 5 of each study phase, a non-fasting blood draw will be taken. The subjects will undergo an fMRI at the end of each phase to assess indices of neuronal activation of brain reward and control centers under food-stimulated conditions. Results of the proposed study will determine whether SR can lead to weight gain, answering the key question of causality. Furthermore, data will be able to generate novel hypotheses related to the role of sleep duration

and energy balance on cardio-metabolic risk profile and results may provide additional knowledge on which to base public health recommendations for obesity prevention efforts.

Lay Abstract:

Chronic sleep restriction (SR) is highly prevalent in today's modern society. Artificial light, portable electronic devices and 24 hour services have allowed individuals to remain active throughout the night, leading to reductions in total sleep time. Our current state of knowledge surrounding the relationship between short sleep duration (SSD) and obesity stems largely from observational studies. People who sleep less weigh more than normal sleepers and are at a greater risk of obesity. However, those studies cannot determine causality and are limited by subjective measurements, such as self-reported sleep duration, which could lead to bias. We are interested in establishing whether sleep could be a cause of obesity. This study will be a randomized, crossover, outpatient study. It will have 2 phases; each phase will be 6 weeks long. After the first phase, there will be a 6 week washout period before starting phase 2. Sixty-six healthy, men and pre-menopausal women at risk of overweight and obesity, age 20-40 y, who are currently normal sleepers, will be recruited. After an initial screening visit, they will wear an actigraph monitor for 2 weeks prior to beginning the study to monitor their sleep and determine if they are normal sleepers (sleep 7-9hours/night). Then, they will be randomized (like a flip of a coin) to either 1 of 2 phases: habitual sleep (HS) or sleep reduction (SR). During the HS phase, subject sleep duration will be their regular bed and wake times. The SR phase will be their HS time minus 1.5 h. For example, if the participant's habitual sleep is 8 h/night and they go to bed at 11:00pm, then during the SR phase they will sleep for 6.5h/night and go to bed at 12:30am. At the beginning and end of each study phase participants will have their height, weight, and waist and hip circumference measurements recorded, a blood sample taken, and body composition assessed using magnetic resonance imaging (MRI). Body weight and waist circumference will be measured weekly, fasting blood and urine samples will be taken at baseline, week-3, week-4, and endpoint, during adherence check visits. Sleep and physical activity level will be recorded using actigraphy and assessed weekly. At week 4 of each study phase, a dose of doubly-labeled water (DLW) will be given to measure how many calories the subjects burn during regular day-to-day life. At week 5 a non-fasting blood draw will be taken during adherence check visit. An fMRI will be done during week 6 of each study phase to look at neural responses to food stimuli. Given the increasing prevalence of obesity over the past 5 decades, coinciding with the marked reduction in sleep duration, further exploration into the role of sleep as a risk factor for obesity could provide additional ammunition in the fight to prevent further increases in the incidence of obesity.

Risks, Benefits & Monitoring

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:

Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in past studies should be provided.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The major potential risks in this study are related to the sleep restriction, blood draw, and the MRI/ fMRI.1. Risks associated with SR:Participants may feel sleepy and irritable during the SR phase. They may feel drowsy, less attentive, or have difficult concentrating.2. Risks associated with blood drawing:At the baseline visit and weeks 3, 4, 5, and 6, routine venipuncture will be performed for screening laboratory studies, and on the oral glucose tolerance test days, an antecubital vein catheter will be inserted in one arm for multiple blood sampling. Drawing blood and inserting an intravenous line into an arm vein are safe and standard medical procedures. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture. The volume of blood collected during this study will be no more than 30 mL per time point. This is not expected to have any serious negative effects on a study participant.3. Risks associated with MRI and fMRI scanning:There are no significant risks associated with the use of MRI except the risk of flying object in the magnetic field. MRI scanning involves the use of a magnet and radio frequency waves (much like an ordinary short-wave radio).-There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency signals used in this study, other than the potential risks associated with the scanning procedure summarized below.-MRI uses a strong magnetic field to create images of the body. Because of the strong magnetic field, the greatest risk is that a metal object could be pulled into the scanner and hit someone.-Some people may feel confined and experience anxiety in the scanner.-The scanner produces tapping sounds during operation, which may reach very loud levels.-In extremely rare cases, a magnet can lose its magnetism, in which case cooling fluids may be released noisily through escape valves and may collect in gas form in the scan room. The gas is not harmful in itself as long as fresh air is available.-Some subjects may experience muscle twitches or tingling sensation and/or a slight increase in body temperature during some types of scan activity. These are very unlikely under current guidelines.

Potential Benefits:

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

There is no direct benefit to the subject participating in this project. The potential benefit to others is the information gained by determining the role of prolonged sleep restriction on energy balance and cardio-metabolic risk profile. If successful, future work using this methodology will increase our understanding of how sleep affects energy expenditure, food intake behaviors, and CVD health markers. The research findings will direct future human mechanistic and clinical translational studies concerning the role of sleep in the development of obesity. This intervention will provide information that will guide public health recommendations in the lifestyle management of chronic diseases, including CVD, diabetes, obesity, and Alzheimer's disease.

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Participants may choose not to take part in this research study.

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

All data will be kept on file coded (de-identified) with a study number and without any specific identifying personal health information. Study data will be stored on password protected, encrypted end-point devices. All paper files will be stored in locked cabinets in the Dr. St-Onge's office. All specimen samples will have unique code assigned to it that cannot be associated with the subject. Imaging data will be stored (de-identified) in a secure computer database that is protected by firewalls and passwords. MRI data will be transferred to the New York Image Reading Center via secure servers. Only personnel immediately involved in the study will have access to study files and documents.

All scans will be reviewed by a Radiologist and any incidental findings will be disclosed to the participant.

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

250

Number enrolled to date:

188

Number enrolled since the last renewal or, if this is the first renewal, since the initial approval:

0

Number anticipated to be enrolled in the next approval period:

0

Does this study involve screening/assessment procedures to determine subject eligibility?

Yes

Target accrual:

79

Number accrued to date:

45

Number accrued since the last renewal or, if this is the first renewal, since the initial approval:

0

Number anticipated to be accrued in the next approval period:

0

Of the number of subjects enrolled, or the number accrued for interventional studies with a screening process:

How many remain on the study?

0

How many are off study?

45

How many completed the study?

36

Have any withdrawn of their own initiative?

Yes

How many?

5

Please explain:

Participant 203 completed phase 1, but withdrew before returning for phase 2 due to the development of an unspecified medical circumstance, unrelated to the study/intervention.

Participants 206 and 208 both withdrew from the study prior to starting phase 2, due to limited availability.

Participants 212 and 214 elected not to return for Phase 2 due to the COVID-19 pandemic.

Have any been removed by PI?

Yes

How many?

4

Please explain:

Participant 102 completed phase 1, but failed to qualify for phase 2 on three separate occasions.

Participant 111 completed phase 1, and returned for phase 2, but was discontinued after 2 consecutive weeks of non-adherence to the intervention.

Participant 209 was disqualified at the second follow-up visit of phase 1, due to non-adherence to the intervention.

Participant 252 was disqualified at the third follow-up visit of Phase 1 due to non-adherence to the intervention.

Have any been lost to follow-up?

No

Have any died while on study?

No

Have any subject complaints been received?

No

Is this a multi-center study?

No

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase

1/2, sub-studies)?

No

Of the number enrolled, or the number accrued for interventional studies with a screening process, indicate:

Population Gender

Females	Males	Non Specific
49%	51%	0%

Population Age

0-7	8-17	18-65	>65	Non Specific
0%	0%	96%	4%	0%

Population Race

American Indian/Alaskan Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	More than One Race	Non-Specific
2%	9%	0%	20%	47%	7%	15%

Population Ethnicity

Hispanic or Latino	Not Hispanic or Latino	Non-Specific
29%	71%	0%

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[ ]Individuals lacking capacity to provide consent

[x]CU/NYPH Employees/Residents/Fellows/Interns/Students

Please ensure that a plan for avoiding elements of coercion or undue influence of these populations is addressed on the Informed Consent page.

[ ]Economically disadvantaged

[ ]Educationally disadvantaged

[ ]Non-English speaking

[ ]Other Vulnerable populations

[ ]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

Two hundred fifty men and pre-menopausal women, age 20-40 y and 55-75 y, BMI 25-35 kg/m2, or with BMI 20-24.9 kg/m2 who have at least one parent who has ever had a BMI >27 kg/m2, will be recruited from the New York City area (target accrual: n=79). These individuals are considered at risk of obesity, making this study group relevant for obesity prevention efforts. Participants who will be recruited to participate in this study will habitually sleep 7-9 h/night, will be free of any current and past sleep and psychiatric disorders, including eating disorders (ex. anorexia, bulimia, night eating syndrome), and will not have diabetes or CVD, and have normal scores on all screening questionnaires. Participants with resistant hypertension will be excluded.

Does this study involve compensation or reimbursement to subjects?

Yes

Describe and justify reimbursement/compensation:

subject compensation of $2000 (older adults) or $2400 (younger adults) will be provided

Are subjects eligible for compensation of $600 or more in a calendar year?

Yes

Subjects qualifying for compensation of $600 or more in a calendar year will need to complete a W9 form and provide their social security number for IRS reporting purposes. If your study includes more than $600 in compensation in a calendar year, the following should be added to the consent document: According to IRS regulations, payments totaling more than $600 in a calendar year will be reported to the Internal Revenue Service (IRS).

Attached Attestation

Principal Investigator	Date Created
Marie Pierre St Onge (ms2554)	10/11/2023

Attached HIPAA Forms

Number	Type	Title	Status
AAAN3095	A	NIH sleep restriction	Approve

Attached Consent Forms

Number	Copied From	Form Type	Title	Active/InActive	Initiator
AACR3450	AACR3450	Consent	NIH Sleep Restriction	Active	Marie Pierre St Onge (ms2554)
AACR3500	AACR3500	Consent	NIH Sleep Restriction	Inactive	Marie Pierre St Onge (ms2554)

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	DSMP	Data Safety Monitoring Plan	Data_Safety_and_Monitoring_Plan.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 1 to MD	Email/Communication/Message	MRI Findings Level 1 to MD.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 1	Email/Communication/Message	MRI Findings Level 1.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 2 to MD	Email/Communication/Message	MRI Findings Level 2 to MD.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 2	Email/Communication/Message	MRI Findings Level 2.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	MRI Findings Level 3 to MD	Email/Communication/Message	MRI Findings Level 3 to MD.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 3	Email/Communication/Message	MRI Findings Level 3.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 4 to MD	Email/Communication/Message	MRI Findings Level 4 to MD.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	MRI Findings Level 4	Email/Communication/Message	MRI Findings Level 4.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	Administrative Supplement protocol	Funding/Grant Application/Subcontract	St-Onge Administrative Supplement Complete.docx	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	St-Onge PA-13-302 FINAL	Funding/Grant Application/Subcontract	St-Onge PA-13-302 FINAL.pdf	Y	No	06/09/2016	Marie Pierre St Onge (ms2554)
No	Actigraph Monitor Manual	Investigator Brochure/Package Insert/Device Manual	Actiwatch Manual.pdf	Y	No	09/06/2016	Theresa Pizinger (tmp2125)
No	Material Transfer Agreement	Material Transfer Agreement	MTA-Out_Request_Form.pdf	Y	No	06/09/2016	Theresa Pizinger (tmp2125)
No	PSQI validation manuscript	Other	Buysse 1988 PSQI validity.pdf	Y	No	05/15/2017	Marie Pierre St Onge (ms2554)
No	CITI Training Certificate, Jeane Cadiou	Other	CITI Training Certificate, Jeanne Cadiou.pdf	N	No	05/09/2017	Ismel Salazar (is2527)
No	PVT Screenshots	Other	PVT Screenshots.pdf	Y	No	01/19/2017	Ismel Salazar (is2527)
No	HIPAA Fax cover	Privacy and Security Agreement	Facsimile HIPAA Compliant for MRI letters.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	NIH Progress Report, Year 1	Progress Report	Year 1 Accomplishments.pdf	N	No	05/09/2017	Ismel Salazar (is2527)
No	Year 3 Progress report	Progress Report	Year 3 Progress report.docx	N	No	03/05/2020	Justin Cochran (jc5392)
No	Y3 Progress report	Progress Report	Year 3 Progress report.pdf	N	No	04/19/2019	Marie Pierre St Onge (ms2554)
No	Year 5 Progress Report	Progress Report	Year 5 Progress report.docx	Y	No	01/25/2022	Mehreen Bhatti (mzb2107)
No	advertisement	Recruitment Material	Advertisement craigslist.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Flyer, Men	Recruitment Material	NIH - Flyer, Men (Contact Ismel).pdf	Y	No	10/19/2016	Ismel Salazar (is2527)
No	Flyer, Men+Women	Recruitment Material	NIH - Flyer, Men+Women (Contact Ismel).pdf	Y	No	10/19/2016	Ismel Salazar (is2527)
No	NIH Flyer, Younger adults (Contact Mehreen)	Recruitment Material	NIH - Flyer, Men+Women (Contact Mehreen).pdf	Y	No	01/17/2019	Corinne Grady (cg3048)
No	NIH Flyer, Older adults (Contact Mehreen)	Recruitment Material	NIH - Flyer, + , 55-75 y-o (Contact Mehreen).pdf	Y	No	01/17/2019	Corinne Grady (cg3048)
No	NIH - Flyer, + , 55-75 y-o (Contact team gmail)	Recruitment Material	NIH - Flyer, + , 55-75 y-o (Contact team gmail).pdf	Y	No	08/31/2018	Ismel Salazar (is2527)
No	Print Advertisement, Men	Recruitment Material	NIH Advertisement craigslist, Men (Contact Ismel).pdf	Y	No	10/19/2016	Ismel Salazar (is2527)
No	Print Advertisement, Men+Women	Recruitment Material	NIH Advertisement craigslist, Men+Women (Contact Ismel).pdf	Y	No	10/19/2016	Ismel Salazar (is2527)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	NIH Advertisement craigslist, younger adults	Recruitment Material	NIH Advertisement craigslist, Men+Women (Contact Mehreen).pdf	Y	No	01/09/2019	Corinne Grady (cg3048)
No	NIH Advertisement craigslist, older adults	Recruitment Material	NIH Advertisement craigslist, Men+Women Older Adults (Contact Mehreen).pdf	Y	No	01/09/2019	Corinne Grady (cg3048)
No	Print ad Younger adults	Recruitment Material	NIH Advertisement craigslist, Younger adults.pdf	Y	No	10/04/2018	Marie Pierre St Onge (ms2554)
No	Flyer older adults	Recruitment Material	NIH Flyer Older adults.pdf	Y	No	10/11/2018	Marie Pierre St Onge (ms2554)
No	Flyer younger adults	Recruitment Material	NIH-Flyer Younger adults.pdf	Y	No	10/11/2018	Marie Pierre St Onge (ms2554)
No	Beck Depression Inventory II	Study Material/Instrument	BDI-II questionnaire.pdf	Y	No	01/20/2017	Marie Pierre St Onge (ms2554)
No	berlin questionnaire	Study Material/Instrument	Berlin Questionnaire C2000.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Borg scale	Study Material/Instrument	Borg Scale.pdf	N	No	03/29/2017	Marie Pierre St Onge (ms2554)
No	Caffeine Consumption Questionnaire	Study Material/Instrument	Caffeine Consumption Questionnaire.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	EPWORTH SLEEPINESS SCALE	Study Material/Instrument	EPWORTH SLEEPINESS SCALE.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Basic Screening form	Study Material/Instrument	Form 1 Basic Screening Form.doc	N	No	04/13/2016	Theresa Pizinger (tmp2125)
No	Health History Questionnaire	Study Material/Instrument	Form 10 updated Medical History Questionnaire.pdf	Y	No	09/29/2016	Theresa Pizinger (tmp2125)
No	ModRey	Study Material/Instrument	Hale 2018 ModRey.pdf	Y	No	08/29/2018	Marie Pierre St Onge (ms2554)
No	Medication Form	Study Material/Instrument	Medication Form.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	MoCA	Study Material/Instrument	MoCA-Test-English_7_1.pdf	Y	No	11/11/2016	Ismel Salazar (is2527)
No	ModRey, Alternate	Study Material/Instrument	ModRey - Alternate Form.pdf	Y	No	01/09/2019	Corinne Grady (cg3048)
No	ModRey, Scoring	Study Material/Instrument	ModRey - Scoring Sheet.pdf	Y	No	01/09/2019	Corinne Grady (cg3048)
No	ModRey, Standard	Study Material/Instrument	ModRey - Standard Form.pdf	Y	No	01/09/2019	Corinne Grady (cg3048)
No	ModRey Form A	Study Material/Instrument	ModRey2 - Form A.doc	Y	No	08/30/2018	Marie Pierre St Onge (ms2554)
No	ModRey Form B	Study Material/Instrument	ModRey2 - Form B.doc	Y	No	08/30/2018	Marie Pierre St Onge (ms2554)
No	ModRey Form C	Study Material/Instrument	ModRey2 - Form C.docx	Y	No	08/30/2018	Marie Pierre St Onge (ms2554)
No	ModRey Form D	Study Material/Instrument	ModRey2 - Form D.doc	Y	No	08/30/2018	Marie Pierre St Onge (ms2554)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	morning/evening ness questionnaire	Study Material/Instrument	Morningness and Eveningness in Human Circadian Rhythms.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Anthropometrics Sheet	Study Material/Instrument	NIH - Anthropometrics v2.pdf	N	No	05/15/2017	Ismel Salazar (is2527)
No	Anthropometrics Sheet	Study Material/Instrument	NIH - Anthropometrics v3.pdf	Y	No	07/28/2017	Ismel Salazar (is2527)
No	Anthropometrics Sheet	Study Material/Instrument	NIH - Anthropometrics. pdf	N	No	01/14/2017	Ismel Salazar (is2527)
No	Basic Screening Form v2	Study Material/Instrument	NIH - Basic Screening Form 2019.pdf	Y	No	03/28/2019	Corinne Grady (cg3048)
No	Basic Screening Form	Study Material/Instrument	NIH - Basic Screening Form.pdf	Y	No	01/14/2017	Ismel Salazar (is2527)
No	Borg Scale	Study Material/Instrument	NIH - Borg Scale v2.pdf	Y	No	05/15/2017	Ismel Salazar (is2527)
No	Demographics Form	Study Material/Instrument	NIH - Demographics Form v2.pdf	N	No	05/09/2017	Ismel Salazar (is2527)
No	Demographics Form	Study Material/Instrument	NIH - Demographics Form v3.pdf	Y	No	07/28/2017	Ismel Salazar (is2527)
No	Eligibility Checklist v2	Study Material/Instrument	NIH - Eligibility Checklist 2019.pdf	Y	No	03/28/2019	Corinne Grady (cg3048)
No	Eligibility Checklist	Study Material/Instrument	NIH - Eligibility Checklist.pdf	Y	No	01/14/2017	Ismel Salazar (is2527)
No	fMRI rating scale	Study Material/Instrument	NIH - fMRI rating scale.pdf	Y	No	03/29/2017	Marie Pierre St Onge (ms2554)
No	Food diary	Study Material/Instrument	NIH - Food Diary.pdf	Y	No	03/31/2017	Marie Pierre St Onge (ms2554)
No	Sleep Diary 2	Study Material/Instrument	NIH - Sleep Diary 2017-01-13.pdf	N	No	01/14/2017	Ismel Salazar (is2527)
No	Sleep Diary	Study Material/Instrument	NIH - Sleep Diary v3.pdf	Y	No	05/12/2017	Ismel Salazar (is2527)
No	Stanford Sleepiness Scale	Study Material/Instrument	NIH - Stanford Sleepiness Scale.pdf	Y	No	12/21/2016	Ismel Salazar (is2527)
No	VAS scale	Study Material/Instrument	NIH Form 6 Visual Analog Scale.pdf	Y	No	09/29/2016	Theresa Pizinger (tmp2125)
No	Pilot Questionnaire	Study Material/Instrument	Pilot Questionnaire.pdf	Y	No	05/09/2017	Ismel Salazar (is2527)
No	PSQI	Study Material/Instrument	PSQI .pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	SBNS AE form	Study Material/Instrument	SBNS AE form.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	SF-36 Health Survey	Study Material/Instrument	SF-36 Health Survey.pdf	Y	No	04/13/2016	Theresa Pizinger (tmp2125)
No	sleep diary	Study Material/Instrument	Sleep Diary.pdf	N	No	04/12/2016	Theresa Pizinger (tmp2125)
No	sleep disorders questionnaire	Study Material/Instrument	Sleep Disorders Questionnaire.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Sleep Prescription Form	Study Material/Instrument	SleepRx v2.pdf	Y	No	05/09/2017	Ismel Salazar (is2527)

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	Created By
No	Stress questionnaires	Study Material/Instrument	Stress measures.pdf	Y	No	08/17/2018	Marie Pierre St Onge (ms2554)
No	3 factor eating questionnaire	Study Material/Instrument	THREE-FACTOR EATING QUESTIONNAIRE.pdf	Y	No	04/12/2016	Theresa Pizinger (tmp2125)
No	Updated Exit Form	Study Material/Instrument (tracked)	Form 14 Exit Form UPDATED NIH .pdf	Y	No	06/09/2016	Theresa Pizinger (tmp2125)
No	Basic Screening Form Track Changes	Study Material/Instrument (tracked)	NIH - Basic Screening Form 2019 Track Changes.doc	Y	No	04/25/2019	Corinne Grady (cg3048)
No	Eligibility Checklist Track Changes	Study Material/Instrument (tracked)	NIH - Eligibility Checklist 2019 Track Changes.doc	Y	No	04/25/2019	Corinne Grady (cg3048)

Tasks

Section	Task	Required for submission	Completed	Created By	Date Created
Renewal Information	Please note, for all future submissions, all personnel changes must be detailed and specifically state who is being removed or added. Stating 'personnel have been removed' is not sufficient.	Yes	No	Adrian Reyes Gloss (ar4370)	2024-01-31 11:37:02.0
Personnel	You made changes to the study personnel, however, you indicated in the Renewal Information that no modifications are included in this renewal. Please note that changes in personnel are considered modifications to the study and need to be listed as modifications.	Yes	Yes	Pilar Borvice (pb2913)	2024-01-12 14:15:56.0

Section	Task	Required for submission	Completed	Created By	Date Created
Subjects	The enrollment numbers were not updated since the last renewal. For example, last year and this year, the total enrolled is the same (188). In addition, the number of subjects enrolled since the previous renewal is also the same (5). Please review this section and revise all the enrollment and accrual numbers.	Yes	Yes	Pilar Borvice (pb2913)	2024-01-12 14:23:46.0
Documents	Please remove all documents that are inactive, tracked versions, no longer in use or that have been superseded by newer versions. As the enrollment status is listed as closed/data analysis, this includes all consent forms, recruitment materials, or any other subject facing materials. Previous versions of these documents will remain in RASCAL with the submission under which they were approved.	Yes	No	Adrian Reyes Gloss (ar4370)	2024-01-31 11:40:06.0