HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: GLP-1 analogue effects on food cues, stress, motivation for highly palatable foods, and weight

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Version Date: January 24, 2024

(*If applicable*) **Clinicaltrials.gov Registration #:** NCT04779697

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   I usually add only spec aims as that is easy for them to match up for congruency.

   Specific Aim 1: To examine the effects of GLP-1a vs. PBO on food craving, hunger, food-cue- and stress-induced FST intake and eating topography (number of touches, reaches, pick-ups, bites) in the FST.

   Specific Aim 2: To assess the effects of GLP-1a vs. PBO on weekly food craving and food calorie intake in the real-world setting during the 12-14-week treatment period.

   Specific Aim 3: To examine the effects of GLP-1a on metabolic and stress responses (ghrelin, cortisol, and WBISI) on HP food craving and intake in the experimental lab model of food craving and FST intake.

   Exploratory Aim 1: To explore whether the GLP-1a effects on change in HP food cue and stress provoked craving, metabolic and stress responses, and food intake during FST, predict change in 12-week weight outcomes.

   Exploratory Aim 2: To explore whether key individual difference variables of gender, chronic stress, disordered eating, physical activity and diet influence GLP-1a effects on HP food craving and intake responses in the laboratory and in the real-world over the 12-14-week period.

   Exploratory Aim 3: To assess whether any potential change in food craving or food intake are sustained after discontinuation of GLP-1a.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   6 years (5 years for data collection).

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   The United States is at the forefront of the global obesity epidemic with estimates indicating 42% of Americans will have obesity by 2030 (body mass index [BMI] ≥30kg/m2). The obesity epidemic has led to significant increases in rates of obesity-related diseases, including Type 2 diabetes (T2DM), cardiovascular disease, and some types of cancer. To understand the mechanisms driving increases in obesity in humans, the first cycle of the R01 project developed and validated a novel laboratory model for overeating highly palatable (HP) foods in the context of HP food cue and stressful environments, both of which are associated with weight gain and obesity risk. We found that BMI-related adaptations in cortisol, insulin sensitivity, ghrelin, HP food craving and hunger each predicted HP overeating in a Food Snack Test (FST) in a laboratory experiment, and remarkably, these measures also prospectively predicted weight gain over a longitudinal 2-year outcome period. These findings support previous multifactorial models of obesity risk suggesting that BMI-related adaptations in metabolism (i.e. insulin sensitivity, ghrelin), brain stress pathways (i.e. glucocorticoids) as well as in dopaminergic transmission in brain reward pathways (i.e. HP craving, FST intake), interact to facilitate HP overeating and weight gain. The critical next step is to address whether these pathways and dysregulated responses in individuals with obesity can be reversed. Remarkably, recent data suggests that glucagon-like peptide-1 (GLP-1) may modulate stress biology along with its effects on metabolism. Glucagon-like peptide-1 analogue (GLP-1a) medications have established weight loss effects in individuals with T2DM and obesity, but

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specific mechanisms by which they exert their effects on weight are not well studied in humans. Preliminary work led by Dr. Jastreboff indicate GLP-1a decreases craving, hunger and food intake in both the laboratory and real-world setting.

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4. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Overview: Study design overview is depicted in Fig 8. This proposal will enroll community men and women (N=96) with obesity (BMI ≥30-49.9kg/m^2) to evaluate the proposed aims.

Baseline

Participants will participate in baseline assessments [Table 1], a single Food Snack Test (FST) lab day (overview of FST below), and OGTT.

Intervention Phase

Subjects will then be randomized to receive 12-14-weeks of GLP-1a (semaglutide) vs. placebo (PBO) [Fig 8] in a double blind manner. During the intervention, participants will return weekly for blinded medication administration, side effect review, and brief assessments [Table 1]. All study investigators (including MPIs, study MD, study APRN, Coordinator, RA) will be blinded to study group (GLP-1a vs. PBO); only the nurse administering weekly doses of drug or placebo and statistician responsible for randomization will be unblinded. During the last weeks of GLP-1a administration with GLP-1a vs. PBO each participant will again undergo an OGTT and 3-session FST lab days. Overview of FST lab days: The 3-day series of FST Sessions (at the end of intervention) will be conducted on three outpatient days between week 11-14 of treatment under controlled laboratory conditions where subjects are exposed a counterbalanced series of FST without stressor, FST w/ cold-pressor test and FST w/ warm water test (overview of CPT/WWT below). On each day, the provocation will be followed by the FST to assess HP food intake and the sessions will be videotaped for eating topography (ET) assessment. Also, HP food craving, hunger, stress and metabolic measures (ghrelin, cortisol,

Figure 8. Study Design

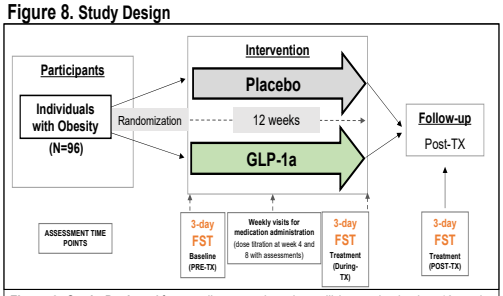

Figure 8. Study Design. After enrollment each patient will be randomized to 12-week intervention with GLP-1a vs. placebo. Assessments will be repeated at time intervals depicted in figure (also see Table 1). Both GLP-1a and placebo have follow-up during last week of intervention. GLP-1a: GLP-1 analogue; TX: Treatment; FST: Food Snack Test

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insulin, glucose, GLP-1) will be assessed at repeated timepoints during each experimental session. All research testers conducting the laboratory sessions will be blind to order of condition.

Post-treatment Follow up

Approximately 1 month (3-6 weeks) after discontinuation of GLP-1a participant will return for a follow up visits which will include FST, labs draw, anthropometric measures, and assessments (as done at the "during treatment" visit (excluding the cold and warm pressor task) (Table 1).

Randomization, Administration and Use of Study Drug (GLP-1a or PBO): The GLP-1a we will use in this study is semaglutide. This long acting GLP-1a is FDA approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, and was recently also approved for the treatment of adults with obesity as an adjunct to diet and exercise. Study drug (GLP-1a or PBO) will be administered subcutaneously by the experienced nurse/clinician at the Yale Stress Center (YSC) or the Yale Center for Clinical Investigation (YCCI)-Outpatient Clinical Research Unit (OCRU), separate from the study team at the Yale Stress Center (YSC). The nurse/clinician will receive the medication in a lock box. All other parts of the visits (side effect review, assessments, etc.) will be conducted at the YSC by the YSC study staff separate from the YCCI-OCRU. In this way, the participant and all other study personnel (MPIs, APRN, study MD, RA, coordinator) will be blinded to GLP-1a vs. PBO. The dose titration will follow the package insert recommendations: 0.25mg subcutaneous injection once weekly for 4 wks; then 0.5mg once weekly for 4 wks; and finally, 1mg once weekly until the end of the study (about 4 weeks) unless clinician feels a slower titration is required due to side effects. If a participant is not able to tolerate the 1mg per week dose (due to GI side effects), we will use the 0.5mg weekly dose. If the participant requires pause of medication for any duration of time (due to medical or other reason), restart and appropriate re-titration will be assessed and determined by study MD, APRN, and PIs. If a subject receiving the 1 mg dose during the last four weeks requires a 13th shot based on when the end of study labs are scheduled, then this injection will be given as 2 shots (0.5 mg each or the equivalent of the PBO) in order to give the prescribed dose. Side effects will be reviewed and assessed weekly by study APRN or MD including the most common adverse reactions (reported in ≥5%) i.e. nausea, vomiting, diarrhea, abdominal pain, constipation.

Lab experiment design: A 1-day experiment is proposed in a 2 (Intervention Group: GLP-1a and PBO) X 3 (Task Condition: FST w/ No Stressor) x2 (Medication Treatment Period: Prex-Tx, During-tx) split-plot factorial design, with Group as the Between-Subjects factor and Task Condition and Medication Period is the Within-Subjects factors. HP food craving, hunger, eating topography, heart rate, blood pressure and biochemical changes in cortisol, ghrelin, insulin, glucose, and GLP-1, will be assessed. Order of sessions will be randomly assigned and counterbalanced across subjects (1:1 randomization). Subjects will also undergo 2 additional experimental FST days during the last weeks of treatment: Cold Pressor Test and Warm Water Test.

General Procedures: Potential subjects will complete initial screening over the telephone/in person to determine eligibility based on inclusion/exclusion criteria. Following screening, eligible subjects will attend intake sessions to obtain informed consent and conduct baseline assessments of physical health with history, exam and blood work. Women aged 55 and under will also complete a pregnancy urine test.[**Table 1**]. If the participant meets inclusion/exclusion criteria, he/she will be scheduled for OGTT, and the pre-tx 3-day FST lab sessions.

Assessments: Assessments as shown in **Table 1** will be conducted in both arms of the study over 12-14-weeks unless otherwise specified, with details of reliability and validation included: **(a) Sociodemographic, health, and social:** Socio-Demographic Indices including age, race, ethnicity, gender, education and occupation level, and socioeconomic status (SES), marital status, housing and working conditions; **(b) FST Sessions:** described in detailed in Section on FST; **(c) Obesity/weight-related measures:** Height will be measured once at the start of the study (with a stadiometer) and will be used for all BMI calculation for the remainder of the study as not to artificially change BMI with inaccurate "change" on height. Each visit will include measure of waist circumference, using standard WHO protocol for consistency. Each visit will include measure of weight,

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percent body fat, and fat mass using the TANITA scale and following the well-established NHBLI and NHANES III protocol. BMI will be calculated from weight and height (weight [kg] / height [m^2]) and via the TANITA scale; Study clinicians (MDs and APRN) will perform the physical exam, review of all vital signs, A1c, laboratories obtained, discuss all details involving the medication administration/side effect assessment/ management of any side effects which may come up, etc. PGA's will administer the PHQ-9 via Redcap and scores will be relayed to study clinicians in real-time; **(d) Dietary intake:** Patients will complete the Nutrition Questionnaire from the NHANES. Food Craving Inventory (FCI) will be used to assess food craving; Real-life dietary intake will be assessed using a 24-hour food recall program. The National Cancer Institute's (NCI) Automated Self-Administered 24-hour (ASA24®) dietary assessment tool will be administered and must be completed on 2 week days and 1 weekend day. Study personnel will call participants to complete the ASA24 over the phone. **(e) Physical activity**: Patients will complete the previously validated Physical Activity Questionnaire (used in Nurses' Health Study). Additionally, the Seven Day Physical Activity Recall (7 Day PAR), an interview-based instrument, used to recall and record moderate to vigorous physical activity (PA) during the previous 7 days, will be conducted to enable calculation of energy expenditure in MET-hrs per week or kcal/kg/day. Assessment will include they type of physical activity, duration, location, and vigor; **(f) Stress:** Stress assessment will be done with the Cumulative Stress/Adversity Checklist (CSC), and the Perceived Stress Scale (PSS) which assess acute and chronic life events that impact health and well-being; **(g) Mental Health:** Depression symptoms will be assessed with the 9-item Patient Health Questionnaire (PHQ9) and anxiety will be assessed with the 7-item scale for Generalized Anxiety Disorder (GAD-7). PHQ-9 is scoring is done in real time, if score concerning MD/APRN informed in real-time to assess whether referral is needed. Participants will be referred for care as is appropriate in a timely fashion. If emergent situation they will be referred to the Emergency Room. If it is not an Emergent situation they will be referred to their primary care provider. Of note, this medication (semaglutide) is not known directly cause or be related to mood change/depression. The reason we have this is because pts with obesity may have depression, so we would like to err on the side of caution. Smoking will be assessed by self-report; **(h) Disordered Eating:** Disordered eating patterns will be assessed using the Dutch Eating Behavior Questionnaire (DEBQ),Eating Disorder Examination-Questionnaire (EDE-Q) and the Emotional Overeating Questionnaire (EOQ); Participants will also be asked to complete the Yale Food Addiction Scale (YFAS) at the screening visit to assess food cravings and consumption and eating behaviors. **(i) Fatigue:** Fatigue will be assessed using the Fatigues Assessment Scale (FAS), a 10-item scale evaluating symptoms of chronic fatigue; **(j) Sleep Quality:** Sleep Quality will be assessed using the Sleep Quality Scale, which measures six domains of sleep quality: daytime symptoms, restoration after sleep, problems initiating and maintaining sleep, difficulty waking, and sleep satisfaction.

(k) Metabolic health: Fasting blood draw for glucose, insulin, cholesterol panel, AST/ALT, lipase, Hematocrit, Thyroid panel with TSH and Total T3, Creatinine and a point of care HgbA1c (to assess average blood glucose level over 3 months) will occur at baseline and during the last week of GLP-1a vs. PBO intervention. Fasting blood draw for glucose, insulin, cholesterol panel, AST/ALT, Thyroid panel with TSH and Total T3, and a point of care HgbA1c (to assess average blood glucose level over 3 months) will occur at the post-treatment follow up visit. All lab samples will be stored in -80 freezers; **(l) Oral Glucose Tolerance Test (OGTT) to assess insulin resistance:** Fasting participants will receive 75g glucose drink orally (Glucola). Intravenous (IV) catheter will be placed and blood samples taken for glucose and insulin at time points -20, 0, 10, 20, 30, 60, 90, 120 minutes. Whole body insulin sensitivity index (WBISI) will be calculated (WBISI=10,000/[$\sqrt{}$(FPG x fasting plasma insulin) x (mean OGTT glucose concentration x mean OGTT insulin concentration)] as a measure of insulin resistance; **(k) Tolerability/safety**: at each weekly visit patients will be asked to report any side effects/issues they may have had with the medication. Additionally, vital signs including BP and HR will be assessed at baseline, during last week of GLP-1a/placebo administration and at the follow-up visit post intervention.

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Table 1. Timing of Assessments/Measures

		Time of Assessments (weeks)			
Domains	**Measure**	**Baseline**	**Follow-up visits during 12-14-week intervention** (weekly)	**During week 11-14 of GLP-1a administration**	**Follow-up (3-6 weeks post intervention**
Demographic, health, and social	Demographics, medical hx, menstrual hx,	X			
Primary Outcomes					
FST w/ no stressor	Food Intake, FCS, hunger (VAS); metabolic measures	X		X	X
FST w/CPT stressor	Food Intake, FCS, hunger (VAS); metabolic measures			X	
FST w/WWT stressor	Food Intake, FCS, hunger (VAS); metabolic measures			X	
Secondary Outcomes					
Obesity/weight-related measures	Weight, BMI, %Body Fat, Fat Mass, WC	X	Xweekly	X	X
Dietary intake (real life)	3-day FD with 24hr recall, NQ, FCI	X	X4,8	X	X
Physical activity	7-day PA record, PA Questionnaire	X	X4,8	X	X
Stress	PSS, CSC	X	X4,8	X	X
Mental health	PHQ9, GAD7, Smoking Status	X	X4,8	X	X

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Disordered Eating	DEBQ, EDE-Q, YFAS, EOQ	X	X4,8	X	X
Fatigue	FAS	X	X4,8	X	X
Sleep	SQS	X	X4,8	X	X
Metabolic health	Fasting glucose, insulin, cholesterol panel, AST/ALT, Hematocrit, Thyroid panel with TSH, Total T3, Cr, lipase, POC A1c	X		X	X[a]
Insulin resistance	OGTT, WBISI (calculated)	X		X	
Tolerability/Safety	Medication side effect	X	Xweekly	X	
Safety	VS: HR, B/P	X		X	X

FST = Food Snack Test; WWT = Warm Water Test; CPT = Cold Pressor Test; FCS = Food Craving Scale; VAS = Visual Analogue Scale; F/S/N = Food, Stress, and Neutral cue; BMI = Body Mass Index; WC = waist circumference; X^{weekly} = weekly assessment; $X^{4,8}$ = assessment at week 4 and 8; PA = Physical Activity; NQ = Nutrition Questionnaire; FD = 3-Day Food Diary; HgbA1c = Hemoglobin A1c; PSS = Perceived Stress Scale; CSC = Cumulative Stress/Adversity Checklist; PHQ-9 = Patient Health Questionnaire; GAD-7 = 7-item scale for Generalized Anxiety Disorder; DEBQ = Dutch Eating Behavior Questionnaire; EDE-Q = Eating Disorder Examination-Questionnaire; YFAS = Yale Food Addiction Scale; EOQ = Emotional Overeating Questionnaire; FAS = Fatigue Assessment Scale; SQS = Sleep Quality Scale Cr = Creatinine; POC A1c = point of care hemoglobin A1c; OGTT = oral glucose tolerance test; WBISI = Whole body insulin sensitivity index; VS = vital signs; HR = Heart rate; BP = blood pressure.

[a]Hematocrit, lipase, and creatinine will not be done at the Follow-up Post-Intervention visit. Fasting lipid, fasting glucose, and fasting insulin level will only be drawn if subject is in the fasting state.

FST Laboratory Experimental Procedures: The laboratory experiment will be conducted in the post-intake in Week 0 prior to medication initiation (pre-tx) with no stressor and again as a series of three FST trials in Week 11-14 (during-tx), but with different and matched no-stressor, CPT and WWT conditions. Cold Pressor/Warm Water Test: We will use an adapted version of the Cold Pressor Test (CPT)/warm water test (WWT), a widely used procedure to provoke mild to moderate pain and stress in both adults and children. It has been used in many studies of pain, autonomic reactivity, and hormonal stress responses. The CPT has been used successfully with both children and adults without reported adverse effects (Von Baeyer et al., 2005; Kowalcyzk et al., 2006; Siegrist et al., 2006; Silverthorn and Michael, 2013). The CPT/WWT includes two conditions presented in random and counterbalanced order: one involving placing their hand and wrist in ice cold water (4 deg C), known as the CPT, or warm water (37 deg C), known as the WWT. The ice cold water stimulus produces a slowly mounting pain of mild to moderate intensity and is terminated by voluntary withdrawal of the limb.

The cold pressor apparatus consists of 2 plastic buckets. One bucket is maintained at 37°C, and the other is maintained at 4°C. Before each cold or warm water immersion, the experimenter will read a standardized script describing the procedures to the participant. Three minutes is the maximum immersion duration per trial, but participants are not informed of the 3-minute limit, and use of wrist watches or other time-pieces is not permitted during sessions. Hand immersion in the water occurs for up to a minimum of 1 trial and a maximum of 3 trials, each with a max time of 3 minutes. Immediately after removing the arm from the cold/warm water, vitals, ratings and blood draws are conducted repeatedly as shown in Table 1.

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Figure 9. Food Snack Test (FST)

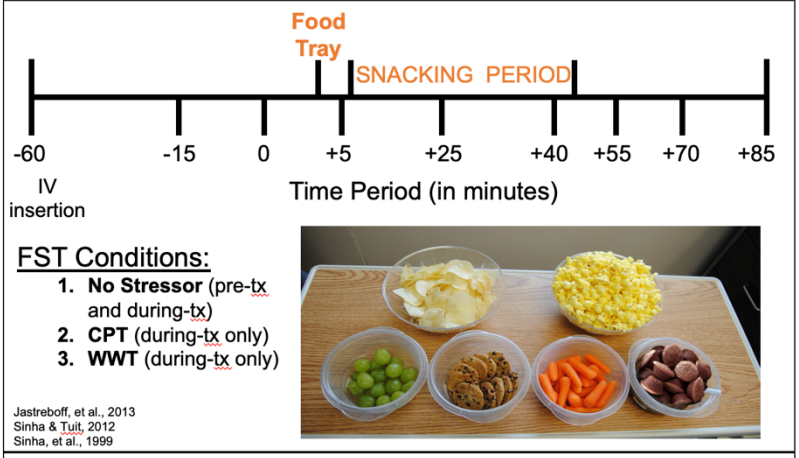

Figure 9. FST experiment day: At baseline participants will undergo an FST with no preceding stressor. They will be presented with a food tray with 6 bowls of food and eat ad libitum for the duration for the 30 minutes. During the last week of treatment with either GLP-1a or placebo, participants will undergo 3 FST with the following conditions: no stressor, CPT and WWT. Food will be weighted before and after food intake period. GLP-1a: GLP-1 analogue; FST: Food Snack Test; CPT: Cold Pressor Test; WWT: Warm Water Test

Laboratory FST Sessions (pre-tx (one day only) and during-tx [3 day sessions during last week of GLP-1a admininstration] and post-tx): On each day, subjects will arrive at the Stress Center at 12:00 after their typical breakfast. They will be provided and consume a standard meal (participants given a choice of bread, meat/protein, cheese, fruit and drink) between 12:00-12:30pm. This will be followed by completion of dietary intake for the current day using the 24-hour food recall and a rest period and then brought into the testing room at 2:00 pm. The staff will document and weigh lunch meal consumed prior to each laboratory session. An indwelling intravenous catheter will be inserted by the research nurse in the antecubital region of the subject's non-preferred arm. A blood pressure cuff will be placed on the subject's preferred arm and a pulse oximeter on the non-dominant forefinger for continuous measurement of heart rate and blood pressure (BP). ***(i) Food Snack Test (FST)*** [Fig 9]: The FST was developed based on previous work on stress and food cue exposure and food intake in the laboratory[176;177;178;179], which indicate that sufficient quantities, multiple food options and sufficient time availability for snacking are important variables modulating food intake. Subjects are presented with 6 bowls of HP unhealthy and healthy food snack (mini chocolate chip cookies, potato chips, mini brownies, buttered popcorn, baby carrots, grapes) each portioned to ~500 calories (3000 calories per lab session). Subject instructions are: "There are 6 bowls of different snacks on the tray. We will leave these here for the next hour and you can eat as much or as little as you like during the next hour". Each bowl will be assessed for total weight and calories consumed for the high and low calorie foods before and after each session. All subjects that consented to videotaping are recorded in each FST session for eating topography assessment. (Subjects sign a separate consent form for this optional videotaping.) **Reliability of the FST:** Data from the current cycle presented in Section 1.2 indicates high reliability of the above procedures in producing food craving and FST intake at Cronbach alpha reliability ranges from 0.84 (laboratory food craving prior to FST) and 0.9 (FST total cal.) and 0.89 (high cal. intake) across the food cue, stress and neutral imagery exposure days. **(ii) Laboratory Assessments:** ***Subjective Measures****: HP Food Craving (adapted from the* Food Craving Inventory (FCI[151]) and data shown in Sinha *et al.,* 2019[73] and in Section 1.2). A total HP food craving score (sum of ratings) and scores for individual items cores are generated for each assessment. *Hunger Ratings*: Subjects also rate their level of hunger on a 10-point Likert scale; ***(iii) Eating Topography:*** Video recordings are assessed for frequency of times each bowl is touched/reached for, frequency of pick-ups and number of bites taken. ***(iv) Physiological*** **Measures:** A pulse sensor will be attached to the subject's forefinger to obtain continuous pulse. Blood pressure will be measured using the Critikon Dinamap 120 Patient Monitor, with multiple measures averaged for each time period of assessment. ***(v) Biochemical Measures****:* Blood samples will be collected as indicated in **Fig 9** and placed on ice immediately after drawing. Within 30 minutes of collection, all samples will be centrifuged at 4C and stored at -80C at the YSC and batch analyzed at the YCCI Core Lab as in our previous studies.

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To help with your comfort and completion of study procedures, we will provide healthy snacks and drinks when it does not interfere with experimental and laboratory sessions.

5. Genetic Testing N/A ☒
   - **A.** Describe
     - i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
     - ii. the plan for the collection of material or the conditions under which material will be received *Write here*
     - iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
     - iv. the methods to uphold confidentiality *Write here*

   - **B.** What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
   - **C.** Is widespread sharing of materials planned? *Write here*
   - **D.** When and under what conditions will materials be stripped of all identifiers? *Write here*
   - **E.** Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
     - i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
   - **F.** Describe the provisions for protection of participant privacy *Write here*
   - **G.** Describe the methods for the security of storage and sharing of materials *Write here*

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

   Subject Characteristics: A community sample of 96 adults aged 18-55 years with obesity (BMI ≥30-49.9kg/m^2) and no other significant medical problems will be enrolled in the study.

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☒ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

   Inclusion Criteria:

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Male and females (1) aged 18-55 years, (2) with obesity (BMI ≥30-49.9kg/m^2) (3) no significant medical problems, including diabetes (potential subjects with a history of gestational diabetes or steroid-induced diabetes may be included at the discretion of the investigator); no history of HgbA1c ≥6.5% (except for subjects with a history of gestational diabetes or steroid-induced diabetes at the discretion of the investigator), (4) English speaking and able to read English and complete study evaluations, and (5) able to provide informed written and verbal consent, (6) able to travel to New Haven CT for weekly visits (over 3.5 to 4 month study duration.

Exclusion Criteria:

(1), Medical status (or concurrent medications) judged by study physician/APRN as contraindication, including but not limited to any significant current medical conditions such as the diagnosis of T2DM or T1DM by American Diabetes Association (ADA) criteria, or untreated gall bladder disease (gallstones), or any psychiatric* or eating disorder, (2) meet current or past DSM-IVR criteria for alcohol dependence or any substance use disorders, including nicotine, (3) current active participation in a weight loss program or weight loss of >10% of total body weight during the prior 6 months, (4) history of prior bariatric/weight loss surgery, (5) taking any other anti-obesity medication, or other medication which impacts weight, (6) history of pancreatitis, medullary thyroid cancer, or MEN syndrome, or (6) women who are pregnant or lactating, seeming to become pregnant, or peri/post-menopausal.

* Given the increased incidence of depression and anxiety in people with obesity, potential subjects with stable anxiety or depression who are treated with non-pharmacology modalities or a stable dose (at least 6 months) of an SSRI (Selective Serotonin Receptive Inhibitor) not associated with significant weight fluctuations will be considered for participation at the PI's discretion.

9. How will **eligibility** be determined, and by whom?

   Eligibility will be determined by the MPIs Dr. Jastreboff and Sinha and by study physician (Kelly Joseph, MD) and APRN (Elizabeth Doyle, DNP, APRN) with oversight from the MPIs (Jastreboff and Sinha)

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

    The potential risks involve: (i) risk associated with physical examination and blood chemistry laboratory testing, IV catheter insertion, for drawing blood and biochemicals during the laboratory sessions; (ii) oral glucose tolerance test (iii) administration and use of study drug (semaglutide or placebo); (iv) imagery exposure to stress and favorite food cues during laboratory sessions; (v) food snack test during laboratory sessions; and, (vi) non-specific risks relating to urine sample and saliva collection and psychological assessments. These are discussed below. The attachment of the blood pressure cuff and the physiological assessments pose minimal risk to the subject.

    (i) Physical Examination, Venipuncture and Other Laboratory Data Collection and Analysis: Subjects will receive a comprehensive physical examination and laboratory blood work to ensure good physical health status. The physical examinations will be conducted by the research nurse who will be well aware of study entry criteria and will manage medical history assessment for this project. Routine laboratory blood work will include glucose, insulin, cholesterol panel, AST/ALT, amylase/lipase, Hematocrit, TSH, Creatinine and a point of care HgbA1c (to assess average blood glucose level over 3 months). Any abnormal findings will be further evaluated by the study physician at the YSC and appropriate medical advice will be provided. These are routine medical procedures and should add no risks other than those normally associated with these procedures. However, the research nurse with advice from the physician on site will ensure that potential participants who

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may be excluded from research due to medical reasons or pregnancy, or those who are in immediate need for medical or psychiatric attention, will be referred to the primary care/psychiatric care facilities in the network so they can receive the appropriate clinical care needed to address their condition. The subjects will be exposed to the risk of venipuncture and intravenous (IV) catheterization during biobehavioral assessments. These are standard medical procedures that are routinely performed in psychobiological research procedures at the Yale Stress Center. Risks associated include local bruising or infection. When an IV is inserted, there is some risk that subjects may develop a bruise where the vein is punctured. If this occurs, appropriate treatment will be instituted immediately. On extremely rare occasions, a blood clot or infection may occur and the YSC is co-located with the Yale Center for Clinical Investigation – Outpatient Hospital Research Unit (HRU-Outpatient) which is fully staffed with nursing specialists, and medical personnel. These risks are mitigated by the use of YSC and HRU research nurses who have extensive experience in venipuncture and IV catheterization. Blood volumes specified below. During each laboratory session, about 80-95ml of blood will be drawn to measure stress hormones during the laboratory sessions. The amount of blood drawn for the tests is equal to about one fourth the blood obtained during a regular blood donation. People who are in good health are not usually affected by this kind of blood loss. However, to be safe, subjects will be warned against donating blood for at least six weeks after completing this study. See Table 2 for the total amount of blood drawn during the study.

Table 2. Total amount of blood drawn

Blood draw during first 6 weeks	**Amount (ml)**
Baseline: OGTT (1)	70
Baseline (pre-tx): FST with no stressor (1)	86
TOTAL throughout study baseline	**156**

Blood draw during following 10-14 weeks	**Amount (ml)**
During-tx: OGTT (2)	70
During-tx: FST with no stressor (2)	86
During-tx: FST with CPT	102
During-tx: FST with WWT	102
Post-tx follow-up FST with no stressor	86
TOTAL throughout study 12-14 weeks (during tx and post tx)	**446**

(ii) Oral Glucose Tolerance Test: The Oral Glucose tolerance test (OGTT) has been used since the 1970s for the diagnosis of diabetes. OGTT enables assessment of insulin resistance and additionally can be used to categorize "at-risk" individuals into categories such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). After an overnight fast, the subject arrives at the laboratory and has a baseline plasma glucose and insulin drawn. He/she subsequently receives 75 g of oral glucose in the form of Glucola (a sugar drink). Blood is drawn at several time points over the next two hours to assess the changing levels of glucose and insulin relative to the glucose ingestion. Outcome measures of the OGTT include: 1) index of whole body-insulin sensitivity (ISI); 2) insulin sensitivity index-glycemia (ISI-gly) – reflective of peripheral insulin sensitivity ratio of change in insulin to change in glucose over the first 30 minutes - which is a measure of insulin secretion (predictive of the development of type 2 diabetes), glucose area under the curve (AUCglucose), insulin area under the curve (AUCinsulin). The risks of OGTT mostly involve those associated with the indwelling (intravenous, IV) catheter. These risks include discomfort/pain, rarely infection, thrombophlebitis, hematomas, and bleeding at the site. Occasionally, subjects may faint or become nauseated when indwelling catheters are placed. During the OGTT procedure itself, subjects occasionally become develop a headache, feel shaky,

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lightheaded, nauseated, or faint. In terms of the amount of blood to be collected, a total of up to 70 cc of blood will be drawn during the OGTT, included in the total blood volumes presented in previous section. We use the Yale-New Haven Hospital (YNHH) standard of care guideline (blood sampling from a peripheral catheter) to re-infuse the blood saline discards. This method is used to prevent physiological anemia. Any symptoms which may occur during the IV catheter placement or OGTT will be addressed appropriately and if further interventions are indicated the proper physician referrals will be made.

(iii) Administration and Use of Study Drug (GLP-a or PBO): The glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1 analogue, GLP-1a) we will use in this study in called semaglutide. This long acting GLP-1a is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and adults with obesity. Study drug (GLP-1a or PBO) will be administered subcutaneously by a trained and experienced research nurse/clinician at a weekly, in-person visit at the outpatient clinical research unit. The study drug will be double-blinded as follows: the medication will be administered at the Yale Stress Center by a nurse who is not blinded. Study personnel will pick up the medication, either GLP-1a or PBO (saline) from Yale's Investigational Pharmacy in a lock box. Only the nurse/clinician administering the GLP-1a or PBO (saline) will open the lock box and know which one it is. The medication will be wrapped in foil and participants will be asked to look away and close their eyes when it is administered. MD or APRN will complete side effect review. The participant and all other study personnel (MPIs, APRN, study MD, RA, coordinator) will be blinded to GLP-1a vs. PBO. The dose titration will follow the package insert recommendations: 0.25mg subcutaneous injection once weekly for 4 weeks; then 0.5mg once weekly for 4 weeks; and finally, 1mg once weekly until the end of the study (4 weeks). If a participant is not able to tolerate the 1mg per week dose (due to GI side effects), we will use the 0.5mg weekly dose. If the participant requires pause of medication for any duration of time (due to medical or other reason), restart and appropriate re-titration will be assessed and determined by study MD, APRN, and PIs. As per the package insert, we will make every effort to administer study drug on the same day each week, at any time of the day, with or without meals; however, the day of weekly administration can be changed if necessary as long as the time between two doses is at least 5 days (>48 hours). If a dose is missed because the participant is unable to come in for a visit, we will administer the study drug as soon as possible within 5 days after the missed dose. If more than 5 days have passed, we will skip the missed dose and administer the next dose as soon as possible. If more than 10 days have passed between doses, study MD/APRN with PIs will determine whether dose re-escalation is required to prevent the potential for GI side effects. In each case, participants will then resume their regular once weekly dosing schedule. The study drug will be administered subcutaneously to the abdomen, thigh, or upper arm, and the injection site will be documented by the research nurse to ensure that a different injection site is used each week when injecting in the same body region. Participants will be excluded if they have any contraindications to GLP-1a (including personal or family history of medullary thyroid cancer of multiple endocrine neoplasia type 2). Side effects will be reviewed and assessed at each weekly study visit including the most common adverse reactions (reported in ≥5%) including nausea, vomiting, diarrhea, abdominal pain and constipation. After starting study drug, participants will be monitored carefully for signs and symptoms of cholecystitis, illeus and pancreatitis. If any are suspected, study drug will be discontinued and appropriate referral for management initiated. Additionally, safety labs will include creatinine (renal function) and lipase (pancreatitis). Participants will also be monitored for injection site discomfort or erythema, increases in heart rate, fatigue, dysgeusia and dizziness. The only risk associated with the use of placebo is a possible injection site reaction. The study MD or APRN will discuss these risks with the participant as part of the informed consent process. Additionally, the APRN/MD will call each participant during the first week of their dose escalation to assess for side effects and address any questions/concerns that may arise. The MD/APRN will also speak with the participant weekly to assess for side effects and address any questions/concerns that the participant may have at that time.

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(iv) Cold Pressor Test/Warm Water Test: This is a widely used procedure in children and adults that induces mild to moderate transient pain and stress. Subjects may voluntarily withdraw their hand from cold water at any time. There are no known residual effects of placing the hand in ice cold water for brief intervals of 90 seconds for up to 3 times.

(v) Food Snack Test: After each condition (no stressor/CPT/WWT) period, the food snack test will be administered, in which subjects are presented with 4 bowls of highly palatable and 2 bowls of healthy food snacks, each portioned to ~500 calories (3000 calories per lab session). Subjects are instructed to eat ad libitum over the course of one hour. All subjects that consented to videotaping are recorded in each session for eating topography assessment, for which each bowl will be assessed for total weight and calories consumed before and after each session. Video recordings are assessed for frequency of times each bowl is touched/reached for, frequency of pick-ups and number of bites taken. A brief 6-item food craving scale will also be administered in addition to a 10-point Likert scale of hunger and the Differential Emotion Scale (DES) to measure emotions and anxiety. Subjects are asked to rate on a 5-point scale the extent to which an emotional word (item) describes the way s/he feels at the current time. Finally, a pulse sensor will be attached to the subject's forefinger to obtain continuous pulse and blood pressure will be measured using the Critikon Dinamap 120 Patient Monitor, with multiple measures averaged for each time period of assessment. Saliva and blood samples will be collected to measure changes in HPA axis stress circadian cycle.(vi) Non-specific Risks: Saliva samples for cortisol assessment should add no risks other than those normally associated with these procedures. Rating Scales, Questionnaire measures are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality. Our past experience with these measures indicates that they are acceptable to subjects. Careful efforts aimed at maintaining confidentiality have been effective in previous research, and only patients' code numbers will be recorded on the forms themselves to protect confidentiality. Medical Treatment for Injury: The consent form will specify that medical therapy will be provided for injuries sustained as a consequence of participation in this research. This can be provided in part through the Yale Center of Clinical Investigation's Hospital Research Unit located at the Yale New Haven Hospital. Should referral to specialists be needed, however, there are no outside funds available to cover the costs.

Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

ADEQUACY OF PROTECTION AGAINST RISKS

a) Recruitment and consent procedures: All subjects will be screened and interviewed by fully trained research staff who will ascertain interest in participating in the current project. If an individual expresses interest, they will receive an explanation of the study, risks, benefits and a description of procedures. All discussions related to study drug will be conducted by a study physician or nurse practitioner. Subjects will be informed that participation in all components of the research is entirely voluntary and that all information collected will be kept confidential. Subjects will be asked to sign the research consent form only if they wish to participate, following resolution of any questions, and following clear indication that the subjects understand the nature of the study and the consent. After obtaining written informed consent for participation in the study, the subject will be enrolled in the study.

b) Protection against risk: All researchers and members of the research team have or will have taken the Human Investigations Training Course either on-line (through the NIH) or in person through the Yale University School of Medicine. All clinical research procedures will be performed by trained staff, at the YSC and YCCI-Outpatient HRU. In addition, all subjects will have health screens reviewed by a physician prior to

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their participation. In the event of an injury, medical therapy will be offered to the volunteer with the cost incurred by the subject's medical insurance carrier.

Confidentiality of all information in the study will be maintained by identifying subjects by code numbers, which are subsequently linked to their data files. No individuals, other than the professionals directly involved in the study will be allowed to read data forms. Investigators will be required to respect the confidentiality code. No subjects are identified by name in any of the published literature and only by code in major data storage areas.

Risk Associated with IV Insertion and Blood Drawing. The risks of bruising, clotting, and infection will be minimized by having venipuncture performed by trained and experienced personnel under sterile conditions. To avoid injury due to fainting, the antecubital vein catheter will be inserted when the subjects are recumbent. The repeated blood draws during OGTT and laboratory sessions will be obtained from an already inserted catheter to minimize discomfort.

Risks Associated with Study Drug (Semaglutide or Placebo): Study drug (semaglutide or placebo) will be administered by a trained and experienced research nurse. Study procedures will follow the package insert recommendations for semaglutide, including instructions for dose titration, proper administration and safety precautions. Participants will be excluded if they have any contraindications to semaglutide or if a study physician or nurse practitioner believes that it would be unsafe for the participant to receive study drug for any reason. Children under the age of 18 and women who are pregnant, lactating or seeking pregnancy will also be excluded given that safety and efficacy have not been established in these populations. After starting study drug, participants will be monitored closely by study physicians and nurse practitioners and will have frequent check-ins to assess for side effects and to address any questions/concerns that may arise.

Confidentiality: Study participation is voluntary and subjects are informed that they are free to drop out at any time without penalty. All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality in regard to collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the Project Director in locked filing cabinets. Only the investigators, MPIs and main sponsor (Drs. Jastreboff and Sinha) will have access to any forms specifying both participant name and subject number. All number coded subjective and biological data will be kept in locked offices with access only to investigators and research staff. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? No children in the trial
c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
    i. Minimal risk
    ii. Greater than minimal

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The following plan has been put in place to ensure safety monitoring during the study.

The principal investigators (MPIs Jastreboff and Sinha) will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigators (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the Yale IRB have the authority to stop or suspend the study or require modifications.

Data Safety Monitor: The Data Safety Monitor for this study will me Dr. Jennifer Sherr MD, PhD. Dr. Sherr is an Associate Professor in the department of Pediatrics (Pediatric Endocrinology) at Yale University School of Medicine. Dr. Sherr is a licensed pediatric endocrinologist with over a decade of experience in conducting clinical trials. Dr. Sherr is very familiar with the requirements for data safety monitoring. She also has several ongoing protocols with the Yale Human Investigation Committee (HIC). Dr. Sherr is not an investigator on the proposed study and would function as an independent monitor.

Dr. Sherr will evaluate all Adverse and Serious Adverse Events, and will assist the MPI's in preparing and sending the pertinent expedited reports to the appropriate persons as outlined. She will monitor the study quarterly and review all adverse event sheets completed during that period. She will assist the MPI's in making critical decisions regarding subject's continuation in the study for safety reasons. She will review the summary of all Adverse Events for this study, which will be reported annually to the Yale Human Investigation Committee (HIC) and the appropriate NIH Project Officer.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Monitoring and Reporting of All Adverse and Serious Adverse Events (AE's): Data on all Adverse Events occurring during the course of conducting the study will be collected, documented and reported by the Project MPIs to the Yale HIC and the NIH Project Officer. A summary of all AE's will be prepared annually, by the project MPIs and the Data Safety Monitor. This will be submitted to the Yale HIC and NIH Project Officer. The Yale HIC requires the re-approval of study protocols at least annually and will not re-approve the protocol without such reports.

Adverse Events (AE) will be defined on the basis of the NIH Guidelines on Data and Safety Monitoring for Intervention Trials. These guidelines define an AE as any reaction, side effect or untoward event that occurs during the course of the clinical study, whether or not the event is considered related to the study manipulations. A new illness, symptom, unfavorable or unintended sign, or worsening of a pre-existing condition or abnormality will be considered an AE. Stable chronic conditions such as asthma that are present prior to study entry and do not worsen will not be considered AEs. For the study, AEs will include events and symptoms reported by the subjects that are of clinical importance as noted by the study staff. The AE Form will be used for recording the event and any follow-up information.

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Attribution of Adverse Events: Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigators (Drs. Jastreboff and Sinha) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

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2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

Reporting of Serious Adverse Events (SAEs): Each AE will be classified by the project MPIs as serious or non-serious and appropriate reporting procedures will be followed. Serious Adverse Events (SAEs) will be defined on the basis of the NIH Guidelines on Data and Safety Monitoring for Intervention Trials. An SAE will be any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, or any congenital anomaly. Any Unexpected Event that suggests a significant hazard, contra-indication, side effect or precaution will also be reported.

The MPIs and study investigators will promptly report all Unexpected, SAEs to the Yale HIC and NIH Project Officer within 24 hours by telephone, and followed by a completed SAE Form within 2 days. The completed SAE Form will include demographic information, a narrative explanation of the event, and photocopies of any relevant source documents from the subject's case report forms. The project MPIs will also address whether there is a need to re-design or amend the protocol, or a need to change the description of risk, either in the consent form or in the protocol.

Reporting of Other Study-Safety Events: The MPIs will inform the NIH Project Officer promptly of any change in recruitment or other changes in the human studies that are relevant to safety, as well as any action taken by the Yale HIC as a result of continuing review of the study. The NIH Project Officer will also be informed of any change in the status of an ongoing protocol, including amendments to protocols, changes in informed consent process, or other problems that could affect the human subjects in the study.

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply): All Co-Investigators listed on the protocol, IRB, and National Institutes of Health.

The principal investigators (Drs. Jastreboff and Sinha) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: NA
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

(i) **Statistical Considerations:** Describe the statistical analyses that support the study design.

Adequacy of Sample Size: Power functions to estimate the required sample size was based on results from the experimental lab model developed and validated in the current project period and from pilot work with the GLP-1a liraglutide study. Large effect sizes were obtained from the effects of GLP-1a Liraglutide study for the following measures (N=6): hunger d=1.3 (before FST) and d=3.0 (after FST); craving d=1.126 (before FST) and d=0.913 (after FST) ; FST Intake: kCal consumed d=0.963 (during FST); FCI d=1.045 (real life); ASA24 caloric intake d=1.182 (real life). Large effect sizes were obtained for greater high calorie% intake in FST for OB vs LN group [Fig 1c] in stress (d=2.94) and food cue (d=4.5) conditions, and moderate effect sizes for cortisol responses predicting FST (f=.35) and in predicting weight gain (f=.32). On the basis of these effect sizes for the laboratory and real world responses to GLP-1a liraglutide and from the current project laboratory data predicting FST calorie intake and weight gain, we selected the large but still fairly conservative (given the above effect sizes of GLP-1a effects) effect size of f=.80 to determine sample size required to detect test the GLP-1a/PBO hypotheses across Aims 1-3. At power=.95, and p=.05, and an effect size=.80, we determined sample size estimates from Cohen to assess Med Group X Condition effects for hypotheses of GLP-1a vs. PBO effects on food craving, hunger and FST cal intake, and for real world FCI craving and ASA 24 caloric intake. At this effect size, we found 15 subjects per Med Group would be needed to detect differential responses due to GLP-1a vs. PBO by condition. However, as no previous study has assessed the effects of GLP-1a on stress and metabolic factors, we used a very conservative effect size=.35, power=.80 and p=.05 and found that a sample size of 33 per med group cell would be needed to detect differences between groups. Furthermore, for the laboratory measures predicting GLP-1a/PBO treated weight outcomes and individual difference measures predicting laboratory and real world weight outcomes, we used an effect size of 0.32 and at power .80 and p=.05, we found that an N=40 per cell (total N=80) would be needed to conduct an initial assessment of lab measures predicting medication effects on weight and in assessment of individual differences. Thus, we propose an N=48 in each group (total N=96), allowing for an attrition of 15% due to drop out, noncompliance or medication intolerance, and expect to have adequate power to test the proposed hypotheses.

Data Management: Procedures for data entry, error checking and quality control have been devised on the basis of our previous experimental and clinical outcome studies. All records are identified by "Day" of testing and not by the type of imagery condition. This allows for all research staff handling data to remain blind to the specific imagery condition. Data are collected using the web-based REDCAP system and quality control and error checking programs are set up for ensuring data integrity. All data will be routinely inspected to assess whether they are missing at random or due to any potential bias, at baseline but especially during the 12-14-week period. If it is not at random, the statistician will include algorithms to account for bias due to missing data. All statistical approaches used to test hypotheses described below allow for missing data points and with provisions to account for bias. These will be applied as necessary.

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Data Analysis Plan: Prior to undertaking the specific analysis for each aim, we will compare PBO vs. GLP-1a groups on demographic and clinical variables using t-tests/chi-square analyses as appropriate. If any group differences are found, the specific variable will be entered as a covariate in all specific analyses. We will also perform relevant psychometric analysis of all laboratory and other assessments for internal consistency and factor structure in our specific subject sample and this will be compared to the established psychometric properties of each measure.

Blinded Analysis of Laboratory Experimental and Food Intake Aims: As specified above in section (i) adequacy of sample size, sample size required for addressing Specific Aims 1-3 is less (N=33 per cell, 66 total) than the requirement of the full project which is estimated to ensure testing of exploratory aims 1-2 pertaining to mechanistic processes predicting weight outcomes (N=80 completers of all aspects). Thus, we will conduct data analysis to address Aims 1-3 as we achieve the subject accrual sample required to test the proposed hypotheses in Aims 1-3. These analyses will be conducted in a blinded manner by the biostatistician and shared only in group composite data without revealing an individual trial medication study assignments so as to maintain the ongoing study blind for all members of the research team. The biostatistician conducts the randomization and is currently not blinded and already has the randomization conditions and thus can perform these interim analyses to ensure progress on accomplishing completion of project aims as data collection is completed for those aims.

For each hypothesis in Aims 1-3, linear mixed effects (LME) models will be used as in our previous laboratory studies. Group 2 (GLP-1a and PBO), Condition 3 (stress, food cue and neutral-relaxing), Tx-Period (pre-tx, during-tx) and timepoint (varying levels, and also assessed by pre and post ad-lib FST food consumption period) will be fixed effects and Subjects will represent the random effect in these analyses. LME models provide an advantage over repeated measures ANOVA analyses as the variance-covariance matrices may be set up appropriately for positive correlations between assessments, and in allowing for missing data points. The exploratory aims will be assessed where laboratory-based processes of food craving, FST intake, WBISI, change in cortisol and ghrelin responses will serve as predictors of weight outcome. Thus, reduction in composite provoked food craving and FST across conditions and change in WBISI, cortisol and ghrelin responses from pre-tx to during-txt will be used to predict change in weight during tx. All analyses will be conducted using the intent-to-treat sample. We will use multi-level models, such as hierarchical linear models (HLMs) and multi-level regression models (MRMs) to explore these aims and assess both the independent and interactive effects of GLP-1a vs. PBO on change in food cue and stress related responses as predictors of weight outcomes. These approaches will also be used to examine if the outcomes vary as a function of gender, chronic stress, changes in diet and physical activity.

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒

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4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. Source: Identify the source of the drug or biologic to be used. Novo Nordisk

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom? Participation in study to be funded by NIDDK/NIH

(b) Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

The medication, Semaglutide, is made by Novo Nordisk.

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Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

(c) Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

Liraglutide, a daily injectable GLP-1 analogue is available for obesity treatment

b) State the maximum total length of time a participant may receive placebo while on the study.

3 months

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.

Possible irritation at injection site.

d) Describe the procedures that are in place to safeguard participants receiving placebo.

The study physician, APRN, or MPI Dr. Jastreboff will discuss these risks with the participant as part of the informed consent process. Additionally, the study MD or APRN will call each participant during the first week of their dose escalation to assess for side effects and address any questions/concerns that may arise. The study MD or APRN will also contact the participant at their weekly, in-person visits to assess for side effects and address any questions/concerns that the participant may have at that time.

(d) Continuation of Drug Therapy After Study Closure ☐Not applicable to this project
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☒ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

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If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   Write here
3. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: 96
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: one site - Yale

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings (Craig's List)	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	

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☒ Other: Yale Stress Center Database

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Individuals can reach out directly to the Yale Stress Center (YSC) after viewing flyers, Facebook and other social media advertisement. They can also be contacted from the YSC data base or YCCI recruitment data base. Finally, as Yale is an op in institution, potential participants can be identified through JDAT with EPIC and emails sent to potential interested individuals. The text for the MyChart message sent out to potential subjects is attached to the protocol.

b. Describe how potential subjects are contacted.

Potential participants will be contacted by phone by trained YSC staff who have extensive experience in participant recruitment.

c. Who is recruiting potential subjects?

The Yale Stress Center (YSC) staff will be recruiting pt. Recruitment of participants will be from the New Haven community through the YSC. Participants will be recruited from the local community, which is ethnically diverse, and we expect that our sample will reflect diversity in the New Haven area. The investigative team have extensive experience in research with this population. The Yale Stress Center has successfully recruited over 900 individuals over the last 5 years from the community through its recruitment strategies and network.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.
Some of the patients may see Dr. Jastreboff or Dr. Kelly Joseph in clinical setting. If patients are offered participation in the study, Dr. Joseph and Dr. Jastreboff will discuss extensively that the patients do not need to participate, that their participation is completely voluntary, and that they will receive the same excellence in care regardless of participation.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment/screening purposes only

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☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

Yale is an opt-in institution, this allows for reaching individuals who may otherwise not know that they are eligible to participate in studies.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data:
as per above

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Recruitment and consent procedures: All subjects will be screened and interviewed by fully trained research staff who will ascertain interest in participating in the current project. If an individual expresses interest, they will receive an explanation of the study, risks, benefits and a description of procedures. All discussions related to study drug will be conducted by a study physician or nurse practitioner. Subjects will be informed that participation in all components of the research is entirely voluntary and that all information collected will be kept confidential. Subjects will be asked to sign the research consent form only if they wish to participate, following resolution of any questions, and following clear indication that the subjects understand the nature of the study and the consent. After obtaining written informed consent for participation in the study, the subject will be enrolled in the study.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The participant will be asked to explain back to the individual preforming the consenting procedures what they will be doing as participant in the study. They will also be asked to verbalize potential side effects of taking semaglutide and will be asked what it means if they are receiving the placebo medication.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-english speaking individuals will not be included in this study.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☒

OR

- Does the research pose greater than minimal risk? YES ☒ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☒ NO ☐

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

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For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☒ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

   Subjects' names will appear only on a consent form and a "key" form kept by the Project Director in locked filing cabinets.

2. How will the research data be collected, recorded and stored?

   All data will be kept confidential except in cases of imminent danger to the participants. Such limits to confidentiality will be clearly explained to participants verbally and in the written consent forms. Confidentiality in regard to collected materials will be maintained via a numbered reference system maintained by the investigators. Subjects' names will appear only on a consent form and a "key" form kept by the Project Director in locked filing cabinets. Only the investigators, MPIs (Drs. Jastreboff and Sinha) and main sponsor will have access to any forms specifying both participant name and subject number. All number coded subjective and biological data will be kept in locked offices with access only to investigators and research staff. Furthermore, good clinical and research practice procedures and HIPAA regulations will be followed.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Laptops and Desktop computers are encrypted by Yale. The Server is also a Yale server. Use of Yale approved REDCAP data collection system.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

   Only deidentified data will be stored. Consent forms will be retained for the NIH and Yale stipulated years after study completion. No plans to destroy the data.

6. If appropriate, has a Certificate of Confidentiality been obtained? A CoC will be automatically provided as this research is NIH funded.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
Subjects may or may not lose weight in this study and this study is not designed to provide subjects with any direct health benefit. We expect that the results of the study, however, may benefit science and others through increasing our knowledge about the mental and physical effects of stress and its relation to behavior.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   They can choose not to participate in the study and try to lose weight in other ways.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   For participation in the study, participants will be compensated as follows: $100 for pre-lab assessments including the baseline OGTT and intake assessments, $100 for each of the 5 laboratory sessions (including at follow-up), $10 for each week of ASA24 dietary recall telephone call $25 bonus for completing all dietary recalls, $20 for each of the visits for injection administration and med check (up to $280), including assessments during specific weeks as per table with $50 for second OGTT, and a $100 bonus for completing all the visits - for a total possible compensation of $1105 for participation in the study. If an injection visit happens on the same day as a lab visit (to minimize trips to the research center for subjects) then the subject will only receive the higher visit compensation (lab visit). Additionally, we will reimburse parking and travel costs for participants. If subjects need to come in for an unscheduled visit, they will be compensated according to the plan above. We will offer to conduct visits during days/times which are convenient for the participant, considering work schedules, child care, etc. The Yale Stress Center staff are trained to treat all participants with respect and caring and to be sensitive to cultural and economic differences.

   Additionally, to facilitate appointment compliance, transportation help to get to the Center and return home will be provided if needed. These may include taxi/uber rides and also reimbursement for gas.

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3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   There will be no costs charged to subjects who participate in this study. All evaluations will be provided at no cost to the subjects. The participants will receive semaglutide free of charge.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs?

      Medical treatment is available through the participant primary care provider, emergency department, or hospital. The study does not provide any medical treatment.

   b. Where and from whom may treatment be obtained?

      Participants primary care provider, emergency department, or hospital care.

   c. Are there any limits to the treatment being provided?

      This would be dependent on participants insurance company as not treatment is provided from the study.

   d. Who will pay for this treatment?

      Any injuries sustained as a consequence of participation in this research, the subject and their insurance carrier will be responsible for the cost of such treatment. Financial compensation for injury is not available. Subjects will be advised that by signing the consent form they are not giving up their legal rights

   e. How will the medical treatment be accessed by subjects?

      By participants primary care provider, emergency department, or hospital care. Subjects will be advised that by signing the consent form they are not giving up their legal rights.

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IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☐

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

APPROVED BY THE YALE UNIVERSITY IRB 2/25/2024