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Document:
Study Protocol

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Official Study Title:
The WISE (Weightloss Intervention Surgical Effects) Brain Study (WISEBrain)

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Protocol

1. **Project Title**: Obesity and Type 2 Diabetes; Bariatric Surgery Effects on Brain Function

   Short Title: ***WISE Brain Function Study*** (Weight Loss Intervention and Surgical Effects on Brain Function.)

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3. **Abstract:**

It is important to highlight the fact that the bariatric surgery intervention itself is NOT a part of this research protocol. The UFHealth Shands Bariatric Surgical Team is operating independently of this study, with regard to decisions involving the suitability of candidates for bariatric surgery. The research team is not involved in any of those patient and physician decisions. Once patients have decided to move forward with bariatric surgery, they will be provided information on the WISE Brain Study, and be given an option of participating in research that will run in parallel to their surgical intervention. This study is designed to examine the effects of the bariatric surgery and resultant weight loss on cognition.

The proposed study will delineate mechanisms underlying the effect of chronic obesity on brain functioning and determine if cognitive benefits of bariatric surgery and weight loss contribute to enhanced cerebral metabolic or hemodynamic function assessed using multimodal neuroimaging methods. The contribution of post-surgical improvements in diabetes-associated insulin-glucose disturbances will be tested. Obesity has reached epidemic proportions and is now a major public health problem, contributing to various comorbid medical conditions, including brain disturbances. There is increasing evidence that chronic obesity may adversely affect the brain, even in the absence of comorbid diseases, such as diabetes, cardiovascular disease, and stroke. We have previously shown that elevated body mass index (BMI) is associated with reduced cognitive function. Increasingly, bariatric surgery is being used as a

treatment for chronic morbid obesity. Besides causing dramatic weight loss in many patients, bariatric surgery alters systemic metabolic and vascular function, including altering insulin and glucose metabolism. Our initial findings from a multicenter longitudinal study of bariatric surgery indicated that people experience improvements in neurocognitive functioning, including memory recall, by 12 weeks post-surgery. These benefits continue over 12 months and relate to not only the amount of weight lost, but also changes in underlying risk factors, such as improved metabolic function, and remission of type-2 diabetes. Neuroimaging provides a potentially powerful biomarker of alterations in brain structure and function (e.g., FMRI), as well as cerebral pathophysiology. To date, no published studies have examined neuronal, metabolic and vascular brain changes following bariatric surgery as proposed in this study. Our preliminary neuroimaging data indicates enhanced functional brain response on FMRI, increased regional cerebral blood flow on arterial spin labeling (ASL), and changes in cerebral metabolite levels on magnetic resonance spectroscopy (MRS). We hypothesize that: 1) Cerebral metabolic and hemodynamic disturbances linked to obesity adversely affect brain function (evident from cognitive testing and FMRI); 2) Weight loss and associated metabolic changes post-bariatric surgery improve brain functions; and 3) Enhanced neurocognitive and neuronal function (FMRI) are due to improved cerebral metabolic (MRS) and vascular (ASL) function. Remission of diabetes is expected to be one factor accounting for these effects, though this effect will also be tied to improved cerebral (MRS) and systemic (e.g., serum cytokines) metabolic health and cerebral perfusion (ASL). A prospective longitudinal cohort matched design will be used to assess changes in these neuroimaging indices, pre- and post-surgery and relative non-surgical obese controls. The groups will have equal proportions of diabetics and non-diabetics with obesity, enabling us to test its influence. By examining obesity and weight loss in the context of bariatric surgery, this study capitalizes on a powerful natural experimental manipulation that can provide a unique window into the effects of obesity and weight loss on the brain.

4. Background:

There is mounting evidence that severe obesity is a risk factor for brain dysfunction. This study examines the effects of obesity on the brain but moves beyond previous research by employing an experimental design to delineate the effects of weight loss following bariatric surgery on brain function and underlying pathophysiology. The proposed study has compelling scientific, clinical, and public health significance.

Public health/clinical significance: **1)** Obesity is a major public health problem contributing to various medical problems that affect mortality and morbidity[26]; **2)** Currently, over 15 million Americans (1 in 20) are severely obese, and the prevalence of severe obesity is accelerating[27]. Severe obesity has major public health and socioeconomic consequences, including increasing health care expenditures[2] , and reducing productivity [28 29] and quality of life (QOL) [30]; **3)** Severely obese people often experience neurocognitive impairments that further diminish health status, health care behavior and utilization, treatment adherence, and QOL; **4)** No study has used neuroimaging approaches to examine whether dramatic weight

loss via bariatric surgery produces changes in obesity-related brain dysfunction; **5)** Evidence of improved brain function post-surgically would motivate future dose-response research to determine whether benefits are achieved from more modest weight loss through behavioral and pharmacological treatments; **6)** Biomarkers of obesity-related brain disturbance may be identified that may inform and enhance future clinical practice, providing additional rationale for aggressively treating obesity in people at risk for brain dysfunction; **7)** Evidence of obesity-associated brain dysfunction may signal a need for interventions to ensure adherence to post-operative behavioral demands.

Adult obesity is highly prevalent and affects health as people age. Millions of obese Americans are now in middle age, a period of life when risk for more serious medical problems increases significantly[31-33]. Obesity affects over 40% of these adults, and severe obesity [body mass index (BMI) ≥ 40 kg/m^2] is increasing at twice the rate of moderate obesity[27]. Severely obese adults have increased risk for co-morbidities, with over 75% developing one or more comorbidities (e.g., diabetes, hypertension, arthritis) with advanced age [27,34-41].

Cognitive dysfunction affects health status, QOL, and treatment adherence. Brain dysfunction occurs secondary to illness that increases mortality, and it adversely affects health status[42-46]. Even mild cognitive deficits affect QOL, diet, physical activity, and other health behaviors[45,47-49], and they are often found to be a stronger predictor of health outcome than other clinical factors[42], but they typically receive less clinical attention.

Obesity-associated metabolic and vascular disturbances contribute to brain dysfunction. Diabetes and vascular disease are among the most common conditions resulting from severe obesity[50-60]. It is now well-established that chronic diabetes and vascular disease contribute to brain dysfunction[19,20,61-68 25,58-60,69-71]. These effects occur even in the absence of large vessel stroke[19,62,65,67], increasing the risk for dementia later in life [14-15,18-20,22]. Accordingly, obesity-associated brain dysfunction has major public health implications as the U.S. population ages and the obesity epidemic continues. This provides a strong rationale for the proposed study.

Cognitive dysfunction affects medical and surgical outcome[42,43,72]. Furthermore, people with cognitive deficits lose less weight following bariatric surgery (see preliminary data; section C.10).

Obesity is a modifiable risk factor for cognitive decline and diminished brain health. Weight reduction has been shown to improve health status and reduce disease risk[73-75]. Our past studies indicate that cognitive functions also improves with weight loss following bariatric surgery (see preliminary data)[17,18,76].

Bariatric surgery is effective and increasingly popular. The prevalence and refractoriness of severe obesity led to bariatric surgery becoming an established treatment for severe obesity [77]. Bariatric surgeries in the U.S. increased over 14-fold (from 13,386 to > 210,000) from 1998 to 2010 [78]. The surgery is an effective method for rapidly producing significant weight loss,

[79-81], as most severely obese patients lose 50% to 75% of their excess weight within two years post-surgery, with many maintaining this weight loss for 10 years or longer [81-86]. Partial or total resolution of comorbidities, including diabetes, tends to occur, along with reductions in mortality.[81,82,84-87]. It may also be cost-effective relative to life-long pharmacological and dietary management [88].

Neuroimaging may provide powerful biomarkers. Neuroimaging has revolutionized neuroscience, facilitating brain-behavior research. Functional magnetic resonance imaging (FMRI) measures brain responses during cognitive-behavioral tasks[89-93]. Arterial spin labeling (ASL) perfusion imaging and magnetic resonance spectroscopy (MRS) enable cerebral blood flow (CBF) and cerebral metabolic dysfunction to be assessed. These MR techniques are noninvasive, have excellent neuroanatomic resolution, and have excellent sensitivity for detecting and measuring subtle functional brain changes over time. Multimodal imaging is being used increasingly clinically, enabling simultaneous measurement of brain structure, function, and pathophysiology. Neuroimaging is relatively inexpensive when performed concurrently and is highly sensitive to treatment effects, [94-102] providing potentially powerful biomarkers for assessing the effects of obesity on brain function and treatment outcomes.

Few neuroimaging studies of weight loss benefits exist. Improved brain health may be possible following weight reduction[16]. Some studies have shown greater white matter integrity[103], as well as improvements on metabolic indices of oxidative stress and glucose metabolism[75,104] and alterations in FMRI brain response on attention-executive and cue reactivity tasks among people who successfully maintained weight loss [105-107]. A few case reports of neuroimaging show adverse brain effects from bariatric surgery, although these cases are not representative[108-112]. Studies of changes in neuronal function (FMRI), cerebral perfusion (ASL), and metabolic function (MRS) following significant weight loss are needed.

Treatment implications. Findings from this study may lead to new strategies for treating and preventing brain dysfunction, perhaps even slowing the onset of neurodegenerative brain changes [26]. Our findings may eventually influence medical decision-making, particularly if the results suggest that rapid and dramatic weight loss reduces subsequent obesity-related brain dysfunction. The results may also signal a need for additional patient education/training to ensure adherence to postoperative behavioral recommendations. Positive findings would also motivate future research focused on dose-response and whether more modest weight loss via lifestyle intervention or pharmacological treatment produces some benefits for brain health.

Scientific significance. The proposed study provides a unique opportunity to examine the effects of severe obesity and surgically induced weight loss on the brain. Past studies of obesity and the brain have largely been either epidemiological or observational. By employing multimodal neuroimaging pre- and post-bariatric surgery, we can

simultaneously assess obesity-associated cerebral metabolite, vascular, and functional disturbances. We will also be able to test the effects of weight loss on brain functions with an approach that can delineate associated cerebral pathophysiology and identify possible mechanisms that cognition improves post-surgery.
We will accomplish several scientific objectives: **1)** The study will provide the most comprehensive information to date on the effects of obesity on cerebral metabolic, vascular, and neural functions; **2**) The longitudinal design will elucidate the trajectory of cognitive change relative to weight loss and changes in diabetes and metabolite-vascular status; **3)** We will determine whether changes in specific risk factors (e.g., diabetes, sleep apnea) mediate these effects; **4)** We will explore the potential value of functional neuroimaging indices as biomarkers of subtle cognitive change; **5)** We will characterize the relationship between systemic and cerebral inflammatory processes by examining both MRS and serum biomarkers; **6)** Bariatric surgery provides a unique experimental approach that goes beyond what can be learned from past observational studies, particularly since significant weight loss will occur relatively quickly and without the intensity of effort required by behavioral interventions; **7)** The scientific significance likely extends beyond obesity, providing insights into mechanisms that may contribute to vascular cognitive impairment and cognitive aging, and perhaps even neurodegeneration.

5. Specific Aims:

A. The proposed study is motivated by four broad objectives:

1. To obtain preliminary multimodal ***neuroimaging*** data on community dwelling adults, including:

   Cohort #1- Surgical Candidates for Bariatric Surgery (BMI>35 kg/m$^{2)}$ the University of Florida, (goal n=120) with Type 2 Diabetes (60) and Non-Diabetic (60)

   Cohort #2- Obese Controls (BMI >35 kg/m$^{2)}$ Individuals ages 20+ in the Gainesville community and North Florida region (goal n=60) with Type 2 Diabetes (30) and Non-Diabetic (30) who will not chose Bariatric Surgery

	Type-2 Diabetes	Non-Diabetic
Bariatric Surgery	N=60	N=60
Obese Control	N=30	N=30

   ***Neuroimaging*:** The rationale for incorporating neuroimaging is relatively intuitive. There is a compelling need for *in vivo* biomarker discovery and validation for the purposes of *in vivo* biomarkers that can be used to assess brain structure, function and pathophysiology, and that may also be predictive of subsequent functional change as people age, as well as responsive to interventions aimed at preventing cognitive decline, MCI and dementia. There is mounting evidence that vascular and metabolic factors contribute to the development of brain dysfunction in the elderly, and that their effects likely begin long before overt symptoms are apparent. A greater understanding of the influence of these and other risk factors on the aging brain is needed, particularly research directed at underlying neuropathological and potentially modifiable mechanisms linked to these factors. The proposed study will provide preliminary data from several neuroimaging modalities that will

be examined relative physical, social, and cognitive functional measures enabling initial examination of the linkages between these behavioral and physical factors, and cerebral metabolic and hemodynamic function, as well as prodromal structural brain changes in those with and without diabetes, before and after a surgical intervention.

2. To collect data on the cognitive module of the ***NIH Toolbox***. (See Appendix D for descriptions and summary screen shots)

   Cognitive assessment: The rationale for collecting cognitive data using the NIH Tool Box was based on two major considerations:

   1) NIA has a vested interest in investigators using the Tool Box in large scale studies and randomized controlled trials of the aging brain;

   2) It was important for purposes of the proposed study to measure cognition at the same time point as the neuroimaging assessment; prior to surgical intervention, 12 weeks post intervention and 18 months post intervention.

   This is a new instrument from those currently being employed. The complete cognitive module of the NIH-Toolbox takes approximately 60 minutes and is computerized.

   Dr. Cohen has attended an NIA sponsored meeting in Washington, D.C, in which the Toolbox was unveiled to researchers to determine its psychometric characteristics, feasibility of use and also to reinforce our willingness to consider this for inclusion in this study. Data obtained to date suggests that it is highly reliable and has validity relative to established neuropsychological tests. The assessment approach's inclusion in this large scale study illustrates its relevance in the mission of studying diabetes and metabolic factors affecting health and functional outcomes.

3. To collect ***blood samples*** from participants for analysis and comparison to other measures previously described.

   We will obtain a serum biomarker panel of cytokines and other molecules sensitive to systemic inflammation, metabolic and vascular pathophysiology. Processing will occur in Dr. Leeuwenburgh's laboratory. Potential analyses using Luminex technology include proteonic analysis on cytokines, inflammatory biomarkers, metabolic biomarkers and neurodegenerative biomarkers. Concentrations of the biomarkers will be examined relative to the MRI indices, particularly the proton MRS cerebral metabolites, providing information the correspondence between systemic inflammatory processes evident in the blood and cerebral metabolite disturbances. The MRS indices (choline (Cho), myo-inositol (MI), N-acetyl aspartate (NAA) and glutamate-glutamine (GLX)) provide information regarding neuronal dysfunction and loss and also inflammatory processes occurring in the brain, as described in our previous studies. A blood sample to measure HBA1C (3 month sugar level) will be sent off to Quest Laboratories, with a de-identified participant number only. Because only the CAM-CTRP billing information and a participant number will be submitted, there will be no opportunity for a billing mistake to take place, which protects the participants. 5 mL aliquots of blood will be sent to Avera in South Dakota for genetic sequencing. The data produced by Avera (digital strings of DNA nucleotides), as well as de-identified demographic and comorbidity data from WISE, will be sent to Sarah Medland laboratory in Australia for further analysis. The genetic sequences that result from these analyses are short fragments of DNA from various genes that have relevance to the WISE study (relation to obesity, cognition, etc.). These sequences do not contain enough genetic information to enable for future identification of specific participants. Blood samples and accompanying data will be labeled with only a de-identified participant label and blood will be discarded as biohazardous waste after analysis. As part of our collaboration, the genetic sequences derived by Dr. Sarah Medland in Australia will be entered into a larger database of the ENIGMA obesity workgroup, which contains similar data from investigators around the

world. This dataset is limited with no PHI, and only a few demographic and clinical diagnostic information.

4. To conduct ***Sleep Apnea Assessments*** at baseline, to account for obstructive sleep apnea effects on neurocognition, for those who have not been previously assessed and assigned CPAP therapy. The Bariatric Surgery program requires most of its patients to have an overnight in-lab sleep study and CPAP therapy prescribed as needed prior to undergoing surgery. The results of the prescribed sleep study will be obtained from the participant's medical record.

B. The specific study aims are as follows: The goal of the proposed study is to delineate mechanisms underlying the effects of chronic obesity on brain functioning, and the basis for improved neurocognitive performance following bariatric surgery induced weight loss. We will use multimodal neuroimaging methods to determine whether these improvements correspond with enhanced cerebral metabolic or hemodynamic functioning following surgery. We will also examine the contribution of insulin-glucose metabolism, diabetes and sleep apnea to these effects.

Aim 1: Demonstrate improved neural function (FMRI) post-surgery compared to obese non-surgical controls. H1: Improved working memory, focused attention and memory recall following bariatric surgery will correspond with increased BOLD response in brain regions of interest (ROIs). On the 2-back working memory paradigm, changes will be greatest in dorsolateral and medial prefrontal cortex (DLPFC and MFC), and the supplementary motor area (SMA). On the CVMT, changes will be greatest in the medial temporal- hippocampal ROIs. **H2.** Post-surgical changes will persist over 18 months. **H3**. Baseline cognitive deficits and FMRI abnormalities, greatest among participants with co-morbid diabetes will improve the most, reflecting effects of bariatric surgery on diabetes and metabolic function.

Aim 2: Demonstrate that cerebral metabolites (MRS) and perfusion (ASL) improve post-surgically. H1: Cerebral metabolite concentrations will improve in hippocampal and frontal ROIs. Decreased choline (Cho) and Myoinositol (MI) and increased N-acetyl aspartate (NAA) will reflect reduced cerebral inflammation (Cho, MI) and neuronal damage (NAA). **H2**) Regional cerebral blood flow (ASL) in these same ROIs will increase post-surgically. **H3)** Cerebral MRS and ASL improvements will be greatest among participants with comorbid diabetes, reflecting benefits of improved glucose metabolism and diabetes status. **H4)** Cerebral MRS improvements will correspond with reduced concentrations of serum cytokines and other pro-inflammatory/neurotoxic metabolites.

Aim 3: Determine whether cerebral metabolite and perfusion effects contribute to enhanced post-surgical cognitive performance and brain function on the FMRI tasks. H1. Cerebral MRS and ASL changes will be shown to mediate enhanced post-surgical neurocognitive and BOLD response. **H2.** MRS, ASL and FMRI neuroimaging, and serum pro-inflammatory biomarker improvements at 3 months will be predictive of 18-month change; **H3**) Post-surgical glucose-insulin changes will also be predictive of improved brain function. **H4)** While reductions in glucose/insulin disturbances will contribute in part to improved neurocognitive and neural function, weight loss itself, and associated changes in cerebral metabolite and perfusion, will be the strongest predictors of improvements in these functions.

Aim 4: We will examine the influence of sleep apnea assessed by ambulatory overnight polysomnography (PSG) on obesity-associated brain dysfunction and improvements following weight loss. A sleep apnea severity index will be derived and used as a covariant in the primary analyses for Aims 1-3.

C. Approach:

Using previously established neuroimaging methods, we will collect *in vivo* MRI measures from participants at the University of Florida McKnight Brain Institute AMRIS facility during a multimodal scanning session in the Phillips 3.0 Tesla scanner, or the UF Health/Shands Siemens 3T MRI Scanner, lasting up to 2 hours, including a short tutorial on the functional task. The primary neuroimaging measures are as follows:

- Structural: cortical and sub-cortical volumes (MPRAGE), white matter hyper-intensity volumes (FLAIR), measure of white matter integrity (DTI)
- MRS: choline (Cho), myo-inositol (MI), N-acetyl aspartate (NAA) and glutamate-glutamine (GLX)) obtained from two primary reagents of interest
- ASL: cerebral blood flow measured from the hippocampus and frontal cortex
- fMRI - Active cognitive tasks: continuous visual memory test, working memory test, visual matching to sample and others. We will perform FMRI using echo planar BOLD imaging (EPI) methods, with data acquired concurrently with ASL

Data from this assessment will provide information regarding brain structural, metabolic/physiological and functional disturbances.

Neurocognitive function will be examined relative to each neuroimaging modality using statistical modeling methods to determine the extent to which they predicts performance in specific cognitive domains (learning-memory, attention-executive, motor-processing speed).

We will also collect a blood sample (approx. 2 TBSP) at the time of the cognitive assessment or MRI visit, which will be stored and analyzed by Dr. Leeuwenburgh's laboratory in the Institute on Aging (IOA) in collaboration with Dr. Cohen to examine how cerebral metabolite abnormalities on MRS (Magnetic Resonance Spectroscopy) correspond with cytokine, ceramide, DNA markers and other metabolic disturbances common to degenerative disease processes.

6. Research Plan:

A. Participant Cohorts and Recruitment- We will recruit 200 adult participants (men = 100; women = 100; age: 20-75 years) to obtain and retain an eventual study sample of 180 severely obese adults. The sample will include 120 people from the UF Bariatric Surgery Service undergoing Roux-en-Y Gastric Bypass (RYGB) or gastric sleeve surgery. We will recruit the non-obese controls from the general community. We will recruit *both the bariatric surgery* and obesity control groups so that approximately 50% of each will have a medical history and current diagnosis of type-2 diabetes based on ADA diagnostic criteria.

	Type-2 Diabetes	Non-Diabetic
Bariatric Surgery	N=60	N=60
Obese Control	N=30	N=30

All participants will be informed that the study involves a cognitive assessment, a physical activity questionnaire and assessment, a few cognitive screening measures, the NIH Toolbox of computerized measures, then an MRI session to record images of their brain, and that this will be repeated for a total of 3 study times, Baseline (or Pre-Surgery), 12 weeks, and again between 9 and 18 months Post-Surgery. (See table 1 for details) During the MR session, participants will rest passively in the scanner and also perform approximately 15 minutes of thinking tasks involving attention and memory. They will also be asked to provide a small blood sample (approximately 2 TBSP) for serum biomarkers and blood glucose.

a. Cohort #1- The surgical candidate group will be presented with the information about the WISE Brain Study, by Recruiting Flyer and if they are interested in participating, will be asked to contact the Program Coordinator, or Recruitment Specialist for more information and screening for the study. In order to undergo bariatric surgery, patients attend an informational bariatric seminar before scheduling a consultation appointment. Patients may be presented information about the study during the seminar but will not be enrolled until after their bariatric consultation appointment. See Appendix NN for the bariatric seminar PowerPoint presentation.

b. Cohort #2- This group consists of community dwelling obese residents who will not undergo bariatric surgery. Participants will be recruited from the Gainesville area and the North Florida region (target n= 60) by the means of advertisement via IRB approved flyers or by mailing IRB approved letters or postcards and posting on local physical and digital bulletin boards of interest, and newspaper classified ads. Groups may also be recruited by short educational seminars on current research in cognitive aging, with recruitment information made available at the end of the talk. Participants will also be recruited at community events with IRB-approved flyers, and participants will have the option to confidentially provide name, phone number, and email if they wish to be contacted by the study team to determine study eligibility. The contact information will be securely stored during the event and immediately stored in the Cohen Lab per study data safety management plan. In the event that a participant recruited from the bariatric surgery clinic consents to participate but does not have surgery, the participant may be switched to the community cohort.

In addition, participants may be recruited from:

- The Claude D. Pepper Recruitment Registry
  PI – Dr. Marsiske, IRB # 415-2007
- HealthStreet, IRB # 265-2011
- CAM-CTRP Consent to Contact Registry IRB #133-2013

B. ***Inclusion and Exclusion Criteria:***

The inclusion criteria for this sample will be aged 20-75yrs. and up, able to walk with or without assistance, with BMI >35, with or without diabetes.

Exclusion of people with pre-existing neurological or psychiatric brain disorders, or MRI exclusions, or diagnosis with a neurodegenerative brain disease like dementia or Alzheimer's or:

(1) Prior neurological disorder (e.g., dementia, stroke, seizure disorder, traumatic brain injury);

(2) Montreal Cognitive Assessment (MoCA) score < 17

- For cases in which score is between 17 and 22, Dr. Cohen (PI) will evaluate assessment results and clinical information to make a determination of whether there is evidence of dementia or early neurodegenerative disease. If the data suggests dementia or other neurodegenerative disease, participants will be excluded and referred to the appropriate clinical care.

(3) Major psychiatric disturbance (e.g., schizophrenia, chronic intractable depression, substance abuse);

(4) Severe CVD history based on criteria described below (e.g. coronary heart disease, coronary revascularization procedure, peripheral vascular disease);

(5) Unstable medical conditions (e.g. cancer; basal cell skin and limited prostate cancer are acceptable);

(6) MRI contraindications (e.g., pregnancy, claustrophobia, metal implants, circumference > 60 cm, weight > 550 lbs); Additional criteria involve being eligible for a MRI scan; People who have metal implants, who are claustrophobic, or do not meet other standard MR safety screening criteria per screening form (Appendix A) will not be included in the MRI portion of the study.

(7) Females of child-bearing potential (younger than 62 years old and no previous hysterectomy) will be screened for pregnancy prior to each MRI session (using urine hCG pregnancy test) and women whose test results read as "positive" will be excluded from study participation.

(8) Physical impairment precluding motor response or lying still on back for 1 hr.

Participants who cannot participate in the MRI due to weight/size limitations will be temporarily excluded from that portion of the study and will be asked to complete only the cognitive assessments, physical tasks, and blood draw at the baseline visit. These participants will be reassessed for MRI eligibility at the 12-week follow-up visit. No MRI data will be collected from participants who exceed weight/size limitations after the 12 week follow up.

C. ***Safety monitoring****:* All participants will be screened for MRI safety prior to undergoing MR imaging, or entering the MR suite. The subject safety screening documents utilized at the University of Florida Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility and UFHealth/Shands are attached as Appendix A to this proposal, and will be used as a screening tool for the study.

D. ***Referrals:***

- **a. MRI findings:** If any questionable findings are noted on the MRI scan by the study team, the study's PI will be notified. The study team and/or PI will contact participants to notify them of the incidental findings, provide them with copy of their MRI scan and will encourage follow-up with their primary care physician.
- b. **Mental Health Issues:** If any assessments or conversations with participants indicate depression, or other new mental health or cognitive functioning concerns, they will be immediately reported to the PI, and the PI will phone the participant to offer referral for appropriate clinical care.
- **c. Post-Surgical complaints:** Should participant discuss any post-surgical adverse events that are related to the surgery, the PI will be notified, and call the participant to encourage follow-up with their clinician, surgeon, or internist, or referrals made as needed.
- d. **Sleep Disorders:** If any sleep disorders are discovered by the sleep study research team, the Sleep Disorder Referral Letter will be sent to the participant. This will strongly encourage the participant to seek additional medical treatment, but will not exclude them from future participation in the study. See Appendices on Sleep Documents section AA.

E. ***Participant Copy of MR Scan-*** After the long-term follow-up MRI scan, we will provide a copy of the MR scan for participants to keep as a courtesy for their records. Participants are informed on the Informed Consent Form that this scan is not for diagnostic purposes, but for research analysis only, and that no "results" will be made available with the scan. Participants are encouraged to share the scan with their physician to keep on file for their records only.

F. Procedural Sequence for Study Visit:

Study Overview Occurs at baseline, 12 weeks and 9 to 18 months
Recruitment and Screening (baseline only) Recruitment Processes PreScreen Informed Consent Inclusion/Exclusion Screen
Assessment Demographic Information Medical/Psychosocial history Neurocognitive Assessments Psychiatric/Behavioral Measures Pain Questionnaire Sleep Questionnaire Weight loss questionnaire Blood Draw for Biomarkers and Glucose Optional Stool Sample
MR Assessment Anatomical and Functional Brain Scan

a. Potential participants will be pre-screened at the time of their initial contact for information about the study, either over the phone or in a private location Participants may also be contacted by email to set up a phone screening. (See Appendix K- Telephone Pre-Screen and Appendix JJ.2 – Email to Interested Candidates).
b. Potential participants identified in person will be asked to complete the WISE Brain Study Screening Informed Consent in order to begin their participation. This ICF will allow study staff to determine eligibility for the study and schedule study-related visits in coordination with the participants' clinical care. Participants who screen in will be invited back to complete the full ICF and complete the remainder of the study activities.
c. If participant meets all inclusionary guidelines, they will be scheduled for their preferred study visit appointments in coordination with their surgery (if applicable).
d. Participants will be explained the study activities again, and the Full Informed Consent will be reviewed with them in a private location. Participants will have as much time as needed to discuss the information with their friends and family. They will be given time to consider enrollment in the study. They will have many opportunities to ask questions and get those questions answered prior to giving their official consent to participate.
e. After informed consent is documented, participants will be screened for inclusion/exclusion factors, including pregnancy.
f. Participants may have the MRI Measurement Device (See Appendix AA.2 in Misc. Attachments) demonstrated for them to visually see the size of the inside of the chamber of the MRI Scanner. Participants may be asked to try the device on themselves to gain a greater understanding of the size constraints related to the MRI Scan, and to give them a chance to experience the snug fit inside the core of the scanner. If participants can not fit in the measurement device, they will be thanked for their limited participation, and given a $10 pre-paid debit card to thank them for their time and effort.
g. Participants will be given a Medical History evaluation, using the Medical History Form. (See Appendix C)
h. Participants will be assessed on cognitive ability, using the MoCA, CVLT-2, PASAT and Boston naming, commonly used in the assessment of MCI and early dementia, and included on the IRB list of approved Psychological Measures. They will also be administered the NIH Toolbox Cognitive performance measures listed in Table 1 (See Appendix D for samples) This portion will take approximately 3 1/2 hours and thus a portion may be done at the time for their MRI visit.

i. We would like to audio record the cognitive sessions for quality assurance. These recordings are for the examiners to accurately note participant's responses and score assessments. The audio recordings will be securely storage in our study's secure computer system. Only research assistants and coordinators who have conducted the study visit will have access to them. The recordings will be deleted upon their attended use.

a. A research study staff certified phlebotomist will obtain the blood sample. Approximately (2TBSP. or less) of blood will be obtained from each participant and stored for analysis of metabolic biomarker panels, inflammatory and neurodegenerative biomarkers and cytokines, along with genomic analysis. Some of the blood specimens could be sent to study collaborators for further analysis. These samples will be coded and will not have any PHI associated with them. These collaborators will have signed Confidentiality Agreements with UF to secure privacy. You will not get any information back regarding these blood tests; they are only being done for the purposes of this research. De-identified blood samples will be sent to Avera in North Dakota for genetic sequencing. Resulting data, along with de-identified demographic and comorbidity data, will then be sent to Sarah Medland laboratory in Australia, where analyses will be conducted on the genetic sequences to reduce the data to DNA coding of genes that have previously been shown to be of relevance to obesity and cognition. Data and samples will only be labelled with the participant's study ID and blood will be discarded as biohazardous waste after analysis. Genetic sequences derived by Dr. Sarah Medland in Australia will be entered into a larger database of the ENIGMA obesity workgroup. Only de-identified data and sparse demographic and clinical information is entered into the database. We will also look at the sugar levels you have in your blood as a result of your body's processing the food that you eat. Blood specimens will be sent to Quest Diagnostics for this test. The specimens will be coded.

b. Participants may be asked to provide an optional stool sample at baseline, 12-week, and 9 to 18-month follow-up visits. The stool sample may be provided by the participant at any time during the study visit or may be collected at home. If the sample is not returned within 48 hours of its collection, study staff will contact the participant to remind them to return the sample. The sample will be collected using a kit that fits over a toilet, and includes a sterile spatula in which the participant will obtain an approximately 50cc scoop of their stool and place in container included in the collection kit. A biohazard specimen transport bag and a brown paper bag will be provided to ensure proper transport and discretion. Included in the collection kit is the Bristol Stool Chart where participants can identify the type of stool produced during collection.

c. A take home packet of questionnaires may be sent home with participant, to save them time at the study visit. This packet can be returned at their next visit. The take home packet can include items such as:
    i. Medication List
    ii. Baecke- activity survey
    iii. Beck Depression Inventory (BDI-II)
    iv. Charlson Comorbidity survey
    v. CHAMPS- physical activity survey
    vi. Epworth Sleepiness Scale
    vii. SF-36 Lifestyle Activity
    viii. TFEQ Eating Inventory
    ix. Pain Questionnaire
    x. Weight loss questionnaire
    xi. UCLA Loneliness questionnaire
    xii. Trait Anxiety Inventory for Adults (STAI)
    xiii. Eating Disorders Inventory-2 (EDI-2)
    xiv. Binge Eating Scale
    xv. Marlowe-Crowne Social Desirability Scale
    xvi. Master Questionnaire- Revised

The following procedures will take place at the AMRIS Center at the McKnight Brain Institute or the UFHealth Shands Siemens 3T scanner - and can be completed at a separate visit if preferred.

d. Participants will be accompanied by study staff to the UFHealth Shands Siemens 3T Scanner which has a larger bore size, (for larger sized participants) where neuroimaging will be performed for approximately one hour. During the scanning session, brain MRI and MRS data will be obtained using a series of sequences in a pre-constructed imaging protocol: 1) T1 MPRAGE; 2) FLAIR; 3) DTI; 4) MRS-Frontal Voxel; 5) MRS-Hippocampal voxel; 6) ASL; 7) Resting BOLD. ASL and BOLD sequences will be interleaved to reduce the required time.

Participant Retention Plan:

In an effort to maximize study retention, letters and thank you-notes may be sent to a participant's home during follow-up periods or if a participant cannot be reached by telephone to schedule his/her next visit. Participants will be mailed or emailed visit confirmations with directions. See Appendix JJ.

We may also contact participants by phone in order to ask general questions about well-being and ability to continue participation in order to maintain contact during follow-up periods. See Appendix KK.

A newsletter discussing study progress and other potential items of interest to the study population will be mailed quarterly to all enrolled participants. See Appendix LL.

We will offer items stamped with the study logo that may support the participants in their daily lives, particularly post-bariatric surgery, at specific time points throughout the study. See Appendix MM for gift schedule.

G. *Compensation:*

Screen Fail:
If a participant arrives for an appointment, but does not pass the screening measures for the MoCA (score < 20) or the MRI (pregnancy, size, or claustrophobia), they will be given a $10 pre-paid debit card to thank them for their limited participation.

Participation in study activity: Participants that complete the cognitive assessment portion of the visit will be given a $60 pre-paid debit card to compensate them for their time and effort. If they participate in the blood draw, they will also receive a $15 pre-paid debit card to compensate them for time and effort. If they participate in the optional stool sample, they will receive a $15 pre-paid debit card to compensate them for time and effort. Finally, participants that complete the MR portion of the visit will be given a pre-paid debit card for $60 for each scan to compensate them for time and effort. This compensation system will be the same for all 3 times that the participant comes to participate in research, Baseline, 12 weeks Post surgery, and at 9 to 18 months Post Surgery.

Travel: If they have traveled 20 miles or more (one way), they will receive an additional $10 pre-paid debit card at each visit to compensate them for additional gas expense.

H. *Data Storage:* There are 5 areas of data collection which will be stored. All data will be coded to protect the PHI of participants. That coded information will be kept in a secure area, with a locked door.

1. MRI scans/images- These images will be stored on password protected computers and encrypted 4T storage drives. Any DVD disks or memory sticks with image data will be coded, locked in a secure room, and in a locked area. This data will also be stored on secure UF servers associated with the UF HiPerGator system, with all PHI removed.

2. NIH Toolbox Results- This web based program transmits the study identifier coded data directly back to the NIH Toolbox servers, and is not stored locally. The PHI free, coded data is then returned to UF and stored on password protected, encrypted computers.
3. Cognitive Assessments done locally- This data will be coded by study participant number, and kept in a secure location in a locked room. Data may be entered into a Redcap Database system or similar database system for analysis.
4. Blood- The blood will be coded, PHI removed, and be stored in a secure lab area, overseen by Dr. Leeuwenburgh.
5. Stool- All stool samples will be de-identified and labeled only with the WISE Study ID# before transfer to the analyses site. There is not a way for offsite collaborators to link the samples to the participants. Research staff will then place a preprinted label on the stool collection vial with the study ID#.

7. Possible Discomforts and Risks

***Participant Burden**:* Participants will experience at least two study visits at each time point, BL, 12 weeks, and 9 to 18 months, depending on their choice and availability. It will consist of a few cognitive measures, a physical activity questionnaire, approximately 1.5 hour cognitive assessment that includes the NIH Toolbox Cognitive measures, 20 minute physical activity measures, one or two one hour MR imaging sessions with two thinking tasks, and a blood draw. During the MR scanning, several sequences will be obtained while participants passively rest in the scanner. Active fMRI tasks will also be administered though this will be limited to approximately 15 minutes. They may also be asked to fill out questionnaires at home and bring them to their next visit.

MRI: During the MRI procedure, participants will be able to talk with the MRI staff through a radio intercom speaker system, and, in the event of an emergency, they can tell them to stop the scan immediately. Participants will be asked frequently during the preparation and scanning period whether they are experiencing any discomfort, and corrections will be made as necessary.
Participants may experience discomfort during the scanning process due to limited space inside the bore of the magnet. Subjects will be closely monitored and repeatedly checked by the investigators to ensure comfort. Participants may also become uncomfortable from lying still for an extended period of time, or if they do not like to be in close spaces (have "claustrophobia"). Padding with blankets can be used to prevent discomfort while lying in the magnet.
The MRI scanner produces a loud “hammering” noise, which has been reported to produce temporary hearing loss in a very small number of people. Participants will be provided with earplugs to wear in the scanner, and also headphones to reduce this risk and possible discomfort.

Blood Draw: The risks of drawing blood from a vein include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure. These risks will be minimized by utilizing only trained personnel for drawing blood and using sterile and disposable materials.

Stool Sample: The process of collecting a stool specimen, while potentially messy, has no risk beyond normal bathroom activity. Participants will be provided with the stool collection kit and protective material (gloves, etc) at no cost to them. Our research team will provide instructions regarding the process. Persons can either bring the sample form home, or they can provide it during the day of their study visits (using a bathroom at the research facilities). A demonstration kit will be available during the study visit to show the components and staff will also instruct participants on how to properly seal the bio bag to prevent contamination during transportation. Participants may elect to collect the sample at home to reduce embarrassment.

Computer based tests: There is a risk that participants will find memory and concentration tests to be difficult, or frustrating, because it is a new task that they are not familiar with, and may be challenging to

their thinking and memory. Participants may skip any question they do not wish to answer. Research staff will explain what to do and help them do the tasks during their research visit.

***PHI*:** Researchers will take appropriate steps to protect any information they collect about study participants. However, there is a slight risk that information about them could be revealed inappropriately or accidentally. Depending on the nature of the information, such a release could upset or embarrass participants, or possibly affect their insurability or employability. These risks will be minimized by storing study documents in secure locations and electronic files on servers protected by passwords; only authorized personnel will have access to the study documents and files.

***COVID-19*:** Upon arriving at the lab space, researchers will use one of several touchless thermometers to take their temperature. If their temperature is 100.4 degrees Fahrenheit or greater, they will leave immediately and inform the PI. Researchers are required to wear surgical masks and gloves, both of which are available within the lab space. Before beginning a participant visit, researchers will use soap and water to clean any frequently used surfaces, such as door handles and tables. These surfaces will then be sanitized with Clorox wipes; items that can't first be cleaned with soap and water, such as electronics, will only be wiped down with Clorox wipes.

Researchers will greet participants outside the building and ask a series of screening questions to determine if the participant currently has any symptoms indicative of COVID-19, has recently traveled to an area with known local spread of COVID-19, or has come into close contact with someone with a laboratory-confirmed COVID-19 diagnosis. If the answer is yes to any of these questions, the participant will not be allowed to complete their visit until they are tested for the virus. If the participant did travel to a known area of COVID-19, but it was more than 14 days prior to participant examination and the participant is symptom free, the examination will be allowed. Researchers will also measure the participant's temperature using the touchless thermometer. If the participants' temperature is 100.4 degrees Fahrenheit or greater, the examination will not be allowed.

If participants arrive without a surgical mask and gloves, the researcher will provide them with both before entering the building. Researchers and participants will remain 6 feet apart throughout the visit, using red tape marks on the floor to indicate where each person should sit. If either the researcher or participant needs to drink, they will step outside and away from people to remove their mask and drink. If the participant needs to use the restroom, they will be asked to remove their gloves and use new gloves when they return. After the visit, the researcher will again clean the testing room with Clorox wipes, making sure to disinfect any surfaces that they or the participant may have touched. Gloves will be discarded in biohazard bins.

Participants and study staff are required to wear a mask at the UF Health Shands MRI Suite. Researchers will maintain a 6-foot distance between themselves and participants at all times. Study materials, including laptop, laptop bag, joystick for task, etc., will be cleaned with Clorox wipes before and after each participant. Masks will also be required within the MRI scanner; the hospital will provide masks that do not contain metal for participant safety.

8. Possible Benefits:

There are no direct benefits to subjects from participating in this study. Results from this study may benefit future researchers and physicians with the diagnosis and prevention of cognitive decline and other brain pathologies related to diabetes.

9. Conflicts of Interest:

There are no conflicts of interest.

Tables and Appendices:

Table 1- Cognitive Measures and Surveys

Appendix A- AMRIS and UFHealth Shands MRI Procedure Screening Form for study participants
B- WISE Brain Study Inclusion/Exclusion
C- Medical History Questionnaire
D- NIH Toolbox Screenshots & Description
E- Physical Activity Questionnaire - CHAMPS
F- N-back and CVMT task samples
G- Parking directions
K- Telephone Pre-Screening Script
N- MoCA
O-COWA
P- Physical Measures – Six Minute Walking and SPPB
Q- Eating Inventory (TFEQ)
R- Baecke Physical Activity Questionnaire
S- Pain Questionnaire
T- Medical Outcomes, SF-36
U- Medication list
V- Weight Loss Questionnaire
W- Epworth Sleep Scale
X- MRI Appointment Information Form
Y- WISE Homework Letter
Z- Sleep Lab Documents
Z.1 Sleep Lab Map
Z.2 Sleep Lab Directions
Z.3 Sleep Disorder Referral Form
Z.4 PSG instructions
Z.5 PSG Pre-visit instructions
Z.6 PSG Return Agreement

AA- MRI Documents
AA.1 Participant Information
AA.2 MRI Measurement Tool
AA.3 MRI Mock Scanner
BB- Pre-Paid Debit Card Payment Form
CC- Adaptive Rate Continuous Performance Task
DD- UCLA Loneliness Scale
EE- Trait Anxiety Inventory for Adults (STAI)
FF - Eating Disorders Inventory-2 (EDI-2)
GG - Binge Eating Scale
HH - Marlowe-Crowne Social Desirability Scale
II - Master Questionnaire- Revised
JJ – Participant Communication Materials
JJ.1 Thank you card
JJ.2 Email for Interested Candidates
JJ.3 WISE Brain Study Timeline – Community Participant
JJ.4 WISE Brain Study Timeline – Surgical Participant
JJ.5 Letter to be Mailed between Visits 2 and 3
JJ.6 Letter for Difficult to Contact Participants
JJ.7 Final Letter for Difficult to Contact Participants
JJ.8 Reminder card
JJ.9 Letter/Email for Visit Confirmations at CRC
JJ.10 Letter/Email for Visit Confirmations at MBI

JJ.11 Parking and Directions to CRC
JJ. 12 Directions to UF McKnight Brain Instititute
KK – WISE Follow Up Phone Questionnaire
LL – WISE Spring 2017 Newsletter
MM – Gift Schedule and Items
NN – Bariatric Seminar Presentation

Table 1. Activity Summary including Cognitive Measures and Surveys		*Cohort #1 Surgical Candidates*	*Cohort #2 NonSurgical Candidates*
Telephone Pre Screen	Appendix K	✓	✓
Part #1 of Study Visit:			
Pre-Scan Screening & Assessments			
MoCA	Appendix N	✓	✓
COWA	Appendix O	✓	✓
MRI Screening	Appendix A	✓	✓
Pregnancy Test	If required - female <62	✓	✓
Medical Health History	Appendix C	✓	✓
Medication list	Appendix U	✓	✓
Medical Outcomes SF-36	Appendix T	✓	✓
Physical Activity Questionnaire (CHAMPS)	Appendix E	✓	✓
Boston Naming Test	Approved IRB Psych list	✓	✓
CVLT	Approved IRB Psych List	✓	✓
Beck Depression Inventory	Approved IRB Psych List	✓	✓
Stroop	Approved IRB Psych List	✓	✓
Trails	Approved IRB Psych List	✓	✓
Adaptive Continuous Performance Task	Appendix DD	✓	✓
Paced Auditory Serial Addition Test	Approved IRB Psych list	✓	✓
Eating Inventory (TFEQ)	Appendix Q	✓	✓
Baecke Questionnaire	Appendix R	✓	✓
Weight Loss Questionnaire	Appendix V	✓	✓
Home Polysomnography Assessment Instructions	Provided by UF Sleep Study Lab	✓	✓
Epworth Sleep Scale	Appendix W	✓	✓
Physical Measures (6MW, SPPB)	Appendix P	✓	✓
Pain Questionnaire	Appendix S	✓	✓
UCLA Loneliness	Appendix DD	✓	✓
Trait Anxiety Inventory for Adults (STAI)	Appendix EE	✓	✓
Eating Disorders Inventory-2 (EDI-2)	Appendix FF	✓	✓
Binge Eating Scale	Appendix GG	✓	✓
Marlowe-Crowne Social Desirability Scale	Appendix HH	✓	✓
Master Questionnaire- Revised	Appendix II	✓	✓
Blood Draw			
Blood Serum for Biomarkers		✓	✓

All NIH Toolbox Samples:	**See Appendix D**		
Dimensional Change Card Sort	NIH Tool Box – Executive	✓	✓
Flanker	NIH Tool Box – Attention/Executive	✓	✓
Picture Sequence	NIH Tool Box – Working Memory	✓	✓
Auditory Verbal Learning (Rey)	NIH Tool Box – Episodic Memory	✓	✓
Picture Vocabulary	NIH Tool Box – Language	✓	✓
Oral Reading Recognition	NIH Tool Box - Language	✓	✓
Pattern Comparison	NIH Tool Box- Processing Speed	✓	✓
Oral Symbol Digit	NIH Tool Box- Processing Speed	✓	✓
List Sorting	NIH Tool Box- Working Memory	✓	✓
Part #2 of Study Visit:			
Pregnancy Test	If required - female <62	✓	✓
MRI Brain Scan		✓	✓
Functional Tasks in MRI			
Continuous Visual Learning Memory CVMT	See Appendix F	✓	✓
N-Back Measure	See Appendix F	✓	✓

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