NIH INFORMED CONSENT TEMPLATE FOR USE AT THE NIA HARBOR HOSPITAL FOR PROTOCOLS NOT TRANSITIONED TO THE REVISED COMMON RULE

Version 1: 09-27-2019

PRINCIPAL INVESTIGATOR: Dimitrios Kapogiannis, M.D.

STUDY TITLE: Intermittent Calorie Restriction, Insulin Resistance, and Biomarkers of Brain Function

STUDY SITE: National Institute on Aging

Cohort: Healthy Volunteer Adult Consent

Consent Version: 01/30/2020

WHO DO YOU CONTACT ABOUT THIS STUDY?

PI: Dr. Dimitrios Kapogiannis – 410-350-3953 - kapogiannisd@mail.nih.gov

Study Coordinator: Kristy Kessler – 410-350-7319 – kristy.kessler@nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study. You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of the study is to examine effects of two diets on how the brain responds to insulin and some parameters of its function related to Alzheimer's disease. We will assign you by chance to one of these diets and we will ask you to follow it for 8 weeks.

Background

The body makes insulin in response to sugar in the blood. Insulin removes the sugar from the blood so that it can be used for energy. Insulin resistance means that your cells may not be able to respond to insulin normally. Your body tries to adjust by making more insulin. Eventually, your body can no longer keep up with the elevated blood sugars and you develop insulin resistance, which often can lead to diabetes**.**

Insulin resistance increases your risk for developing heart disease and stroke. Some studies also suggest that insulin resistance may increase your risk for developing Alzheimer's disease and memory problems later in life. Recent studies have found that the brain of patients with Alzheimer's disease has insulin resistance even when the entire body does not. We refer to this as "brain insulin resistance".

Calorie restriction means restricting the calories one consumes for some period of time besides what is usually considered normal range. One way to implement calorie restriction is to restrict calories for two days a week and not restrict them for the other five. This is known as 5-2 Calorie Restriction.

In this study, we want to examine the effects of two diets implemented over 8 weeks: 1) 5-2 Calorie Restriction (or 5-2 CR) plus "healthy living" diet and 2) "healthy living" diet alone .We will examine if these diets lower your brain insulin resistance, as well as insulin resistance in the entire body, improve aspects of your cognitive function, and/or change the levels of certain chemicals in your body which are related to Alzheimer's disease. These chemicals are found in your blood and cerebrospinal fluid, a clear fluid surrounding your brain and spinal cord. To understand changes in these chemicals, it is important to know if you carry a gene called APOE ε4 that increases the risk of developing Alzheimer's disease; therefore, we will check your DNA for the presence of this gene. In addition, we will use magnetic resonance imaging (MRI) of the brain to see if the 5-2 CR and "healthy living" diet or "healthy living" diet alone will change how your brain functions at rest and while you perform certain tasks. We will also assess whether physical activity changes from implementing these diets for 8 weeks.

Study Population

About 150 people may take part in this study; we will continue recruiting participants until 40 complete the study. All visits will take place at the NIA Clinical Unit, on the 5th floor of MedStar Harbor Hospital.

Inclusion Criteria

You may be eligible for this research study if:

- You are 55 – 70 years old.
- Your Screening Visit lab tests show that you have insulin resistance.
- You have a body mass index (BMI) greater than or equal to 27 (BMI is a measure that we will calculated from your height and weight).
- You weigh less than or equal to 350 pounds;
- Your Screening Visit memory tests suggest that you do not have clinically significant cognitive impairment.

Exclusion Criteria

You may **not** be eligible for this research study if:

- You have been diagnosed with heart or vascular disease that is considered significant for the purpose of this study. Controlled high blood pressure, minor EKG findings, mitral valve prolapse, and benign heart murmurs are allowed.
- You have been diagnosed with a stroke or other neurological disease.
- You have been treated for substance abuse within the past 6 months or have a positive urine drug test.
- You currently have a thyroid hormone abnormality not controlled by medication or other endocrine disorder.
- You have an eating disorder; significant abdominal disorders or malabsorption disorders
- You have been diagnosed with diabetes and/or are currently take medication for diabetes (pills or insulin).
- Your Screening Visit lab tests show that you have diabetes.
- You have been diagnosed with or believe that you may have repeated episodes of low blood sugar, also known as hypoglycemia.
- You currently take corticosteroid medications by mouth, such as prednisone
- You are found to have Human Immunodeficiency Virus (HIV), Hepatitis B or C virus (HCV or HBV).
- You have a low red blood cell count (hematocrit less than 35% and or hemoglobin less than 11 mg/dl).
- You have abnormal liver function tests.
- You are unable to have an Magnetic Resonance Imaging (MRI) scan because you have a pacemaker, other implanted electrical devices, metal implants, or do not meet the criteria after completing the MRI screening form.
- Your blood tests suggest that your blood has trouble clotting.
- You take a blood thinning medication other than low dose aspirin. (If you take full dose aspirin (325mg), you will be asked to stop taking it for 7 days prior to the lumbar punctures).

- You are pregnant. This study involves Magnetic Resonance Imaging and radiation from X-Rays. It is best to avoid exposure of the unborn fetus to Magnetic Resonance Imaging and radiation.
- You are breastfeeding.
- You do not agree to have your blood tested to see if you have a gene (APOE ε4) that increases your risk of developing Alzheimer's disease

Procedures

Overview

This study requires a screening visit and 5 outpatient visits over about 9-12 weeks. All visits will take place at the National Institute on Aging (NIA) Clinical Research Unit located at the MedStar Harbor Hospital. You will be randomized (like a flip of a coin) into 1 of 2 groups. Each group will follow their group's diet for 8 weeks. No matter which group you belong to, we will provide you with informational materials about "healthy living" and ask you to follow their recommendations. We will review this material with you and provide any necessary clarifications. This published material includes brochures on meal portion control, calories in common beverages, meal substitutions for controlling calorie intake, and other dietary considerations.

1. **5-2 CR group (Group 1)**: You will be asked to follow the "healthy living" diet and not overeat for five days a week for eight weeks. For the other two days of the week, which have to be back-to-back (i.e., consecutive), we will ask you to drink only two shakes (Boost®) each day containing a total of 480 Kcal. You may not eat anything else during the 2 restricted calorie days. You may only drink water, coffee or tea without sugar or artificial sweeteners during those 2 days each week. We will discuss with you which two days' work best for you. We will give you all of the shakes (Boost®) you need during your study visits. Dietary counseling will be provided.

2. **"healthy living" group (Group 2)**: If you are a participant in this group, we will ask you to follow the "healthy living" diet daily for every day for 8 weeks.

After you start on your diet, you will come back to the clinical unit every two weeks: weeks 2, 4, and 6. We will measure your vital signs and weight, draw blood and ask you to complete questionnaires and discuss any problems with your diet.

In addition, we will call or e-mail you every other week (weeks 3, 5 and 7) to provide encouragement, answer questions regarding how you are feeling and to discuss any problems with the diets. For e-mail communications, we will the NIH Secure Email & File Transfer Service:

https://secureemail.nih.gov/bds/Login.do. We will give you instructions on how to access the Service and acquire login credentials.

After 8 weeks on your diet, you will come back to the unit for a final visit. If you belong to the 5-2 CR "healthy living" diet group, this last visit will be scheduled for the first day that you scheduled to start your Boost® shake. If you are in the "healthy living" alone diet group, you may schedule your last visit on any day of your diet at 8 weeks. Finally, we will call and/or e-mail you three days after your last visit to check on how you are feeling.

Screening Visit

You will arrive after fasting at least 12 hours overnight. You may have water. During this visit, one of the study investigators or nurse will review this consent form with you and answer any questions. After signing the consent form, we will collect information about your medical history and you will have a physical exam. You will be asked questions to determine whether you can safely have an MRI. You will also go through the following procedures: vital signs, height, weight, blood pressure, blood draw, and urine testing. This visit will take about 3 hours. About 28 ml (2 tablespoons) of blood will be taken during this visit. Before leaving the unit, we will give you a device that monitors your physical activity called an accelerometer. We will ask you to wear the accelerometer on your wrist for 4 days. We will provide instructions on wearing the accelerometer and returning it back to the unit. We will give you a diary to record your activities.

Baseline Visit

After completing the Screening Visit, if you meet the study criteria you will return within four weeks. You will be asked not to eat anything for 12 hours prior to your visit. You may have water. The following procedures will be done: weight and waist measurements, blood draw, lumbar puncture (LP), mixed meal tolerance test (MMTT), cognitive testing, questionnaires, and a brain MRI.

We will draw about 168 ml (about 2/3 cup) of blood and 15 ml (1 tablespoon) of spinal fluid during this visit.

At the end of the Baseline Visit, we will give you one-on-one dietary advice about "healthy eating." This advice includes suggestions about meal portion size, recent Center for Disease Control recommendations for food servings from specific food groups, and other advice about healthy eating. In addition, we will give you printed informational material, such as leaflets and brochures.

We will assign you by chance (similar to tossing a coin) to one of the two diet groups (5-2 CR "healthy living" or "healthy living"). You will have equal chances of being assigned to each group but will not be able choose which group you belong to. If you are enrolled to the 5-2 CR "healthy living" diet group, you will have the opportunity to taste the Boost® shake and choose a flavor you prefer. We will give you enough shakes until your next visit.

This visit will take approximately 7-9 hours. These procedures may be completed in one or two days (within a week) depending on our Unit's availability for certain tests, as well as your preference.

Visits 3, 4 and 5 (Weeks 2, 4 and 6)

If you belong to the 5-2 CR group, these visits will take place during the second of the two consecutive days you drink the Boost® shakes. If you are in the "healthy living" diet group, you may come in anytime during that scheduled week. You will not eat or drink anything except water for at least 8 hours before your visit. The following procedures will be done: weight, waist measurements, vital signs, blood draw, and questionnaires. This visit will take approximately 1 hour. About 62 ml (4 tablespoons) of blood will be drawn on each of these visits. If you belong to the 5-2 CR group you will be given an adequate supply of shakes until your next visit. For safety reasons, if you lose more than 5% of your body weight in 2 weeks or report any serious symptoms, you may be removed from the study due to health concerns.

Weekly follow-up phone call and/or e-mail

We will contact you every other week (weeks 3, 5 and 7) once you begin your diet to ask you how you are feeling. We will ask you about any problems you may have and offer encouragement.

Week 8 Outcome Visit

This visit will be similar to the Baseline Visit, including vital signs, weight and waist measurements, blood draw, lumbar puncture (spinal tap), mixed meal tolerance test (MMTT), cognitive testing, questionnaires, and a brain MRI. If you have been assigned to the 5-2 CR "healthy living" diet group, this visit will occur on the first of the two days that you drink the Boost® shake.

Procedures during this visit take about 7-9 hours to complete. These procedures may be completed in one or two days (within a week) depending on our Unit's availability for certain tests, as well as your preference.

We will draw about 174 ml (about 3/4 cup) of blood and 15 ml (1 tablespoon) of spinal fluid during this visit.

Before leaving the unit, we will give you an accelerometer. We will ask you to wear the accelerometer on your arm for 4 days. We will provide instructions on wearing the accelerometer and returning it back to the unit. We will give you a diary to record your activity.

Follow-up phone call and/or e-mail

We will contact you within four days after the Outcome Visit to see how you are feeling and discuss any problems.

Your participation in the study will end when you complete wearing the accelerometer.

All procedure in this study are for research purposes only.

Medical history and physical exam

We will review your medical history (including your past medical history, current review of systems, medications and supplements, as well as family history of Alzheimer's disease and dementia) at your Screening and again at Week 8 (Visit 6). A physician or nurse practitioner will examine you. You may also be examined if the study physician feels it is needed at any time during the study. You will change into a hospital gown prior to the physical examination. We will measure and record your height, weight, temperature, blood pressure, pulse rate and respiratory rate. This will take about 40 minutes. Please note that this examination is for research purposes only and does not replace an examination you may receive from your own physician.

Blood work

Blood will be drawn through a needle in your arm or alternatively, through an intravenous catheter (IV); thin plastic catheter placed in your vein using a needle and taped to the skin to hold it in place. We will draw no more than 174 ml (roughly 3/4 cup) of blood at one time and no more than 556 ml (about 2.4 cups) during the entire 12-week study. This meets the NIH guidelines of less than 550 cc (2.3 cups) in an 8-week period. The results of your blood tests will be noted in your NIA medical records (genetic results will not be placed in the medical record). If you do not want this information in your medical record, you should not participate in the study.

Human immunodeficiency virus (HIV) and Hepatitis B and C

As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS in addition to Hepatitis B and C. If you are infected with HIV or

Hepatitis B or C, you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others. We will also tell you how we report a positive HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

APOE genotyping, gene expression and DNA Methylation studies

You will be asked to give 40 ml (8 teaspoons) of blood, saliva for genetic research purposes. The genetic material, DNA, will be extracted from the sample and analyzed. We will test your DNA to determine if you carry one or two copies of a gene called APOE ε4 that increases the risk of developing Alzheimer's disease. Your genetic material, DNA, regularly makes proteins to carry out cell functions; this is called gene expression. Some of your blood will be used to examine changes in proteins caused by the diet you follow. Some of your blood will be used to extract your DNA. Your DNA changes during your lifetime; one of these changes is called DNA methylation. We will examine changes in your DNA caused by the diet you follow.

Urine testing

During this study, we will perform a urine drug screen. If your drug test is positive, you will be told promptly, and you will not be included in the study.

Urine pregnancy testing:

If you are a woman who is able to become pregnant, a urine pregnancy test will be performed at the screening visit and prior to the MRI and fluoroscopic LP procedures at the baseline and outcome visits.

Lumbar puncture (LP) (or Spinal Tap)

For this procedure, you will either lie on your side, curled up with your knees at your chest or you will sit upright. Your lower back will be washed and a local anesthetic will be injected into your back to make it numb (can't feel it), which may sting for a few seconds. A needle will be inserted through the numbed skin and into the space between the bones of your spine. You may feel a sensation of pressure. About 15 ml (1 tablespoon) of cerebrospinal fluid (CSF) will be removed. It usually takes 5 to 20 minutes to collect the CSF. After the fluid is collected, the needle will be removed. The entire procedure should take about 45 minutes. You may get up and move around as soon as your doctor or nurse says you may.

This fluid will be used to look at various chemicals related to Alzheimer's disease and body metabolism for research purposes.

The lumbar puncture will usually be done at the bedside by a qualified licensed NIA Practitioner (Physician or Nurse Practitioner) at the NIA Clinical Research Unit. The bedside procedure is possible when the Practitioner is able to feel by palpation certain bony landmarks on your lower back. If the Clinically Responsible Investigators believe that the procedure would be unsuccessful or if they fail to draw CSF after three needle insertions, the LP may happen under X-ray fluoroscopic guidance.

The lumbar puncture will be done at the Baseline and at week 8 (Visit 6). If your blood-work drawn before the lumbar puncture shows us that your blood might not clot normally, we will not be able to perform the procedure.

X-ray fluoroscopic lumbar puncture

Sometimes this test is done using x-rays to help find the correct placement of the needle. This would be done to help us to see the spinal canal better. This procedure will be the same as described above, except you will lie on your stomach on the x-ray table. This will be done in the MedStar Harbor Hospital X-ray Department by a radiologist.

3-hour mixed meal tolerance test (MMTT)

This test is will be done to see what happens to your blood sugar and hormone levels when you eat a meal. You will not eat or drink anything except water for at least 12 hours before the test. An intravenous catheter (I.V.) will be placed in an arm vein to take some blood before drinking a liquid meal (Ensure-Plus ® nutrition shake). A blood sample will then be taken every 20 minutes for 3 hours. This procedure will take about 3 1/2 hours. About 54 ml (3 ½ tablespoons) of blood will be taken.

5-2 CR group:

You will be asked to follow a "healthy living" diet and not overeat for five days a week for eight weeks. For the other two days of the week, which have to be back-to-back (i.e., consecutive), we will ask you to drink two meal replacement shakes (Boost®) each day. You may not eat anything else during the two restricted calorie days. You may only drink water, coffee or tea without sugar or artificial sweeteners during those two days each week. We will discuss with you which two days' work best for you. We will give you all of the shakes (Boost®) you need during your study visits. Dietary counseling will be provided.

"Healthy living" group:

If you are a participant in this group, we will ask you to follow a "healthy living" diet daily for the entire 8 weeks.

Physical activity monitor (accelerometer)

We will ask you to wear a small (1 x 1 x ¾ inch) portable device as a wristband to measure your physical activity. It gives information about your physical activity and the amount of calories you burn. You will wear the device for 4 days after your Screening Visit and after Visit 6 (Week 8). We will give you instructions on how to wear it and how to mail it back in a pre-paid envelope. While wearing the device we will give you a form (diary) and ask you to write down your activity.

Study questionnaires

You will be asked to fill out questionnaires about your health and how well you are able to do your usual activities. You will also be asked to complete questionnaires about any symptoms you may be experiencing and how you are feeling emotionally during the study. These questionnaires will take about 15 minutes.

Cognitive testing

This testing includes tests of your memory, attention, concentration, and thinking. We may ask you to complete questionnaires, take pen-and-paper or computerized test, and perform simple actions. This will take approximately 1 hour to complete.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of your brain, measure its blood flow and function. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. You maybe be asked to lie still for up to 24 minutes at a time. You will be in the scanner for about 2 hours. A plastic device called a "coil" will be placed over your head. While in the scanner you will hear loud knocking noises, and you will be fitted with earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at any time. You will complete a screening form before you are allowed to perform the MRI and if it is determined that you meet any criteria that would exclude you from the MRI (for example pacemakers and some metal implants) then you will not be able to have this test done.

Functional Magnetic resonance imaging (fMRI)

These tests allow us to see what parts of the brain are used when you do a task. A plastic device called a "coil" will be placed over your head. Before the scan, you will be told about the tasks. You will have the chance to practice the tasks first. There is a computer screen that you can see when you are inside the scanner. The screen will show you the task information. In one task, you will look at words of different colors. For example, "green." You will then press the "green" button. The next task will show you pictures of food. You will be given a series of buttons to use to rate how much you do or do not like each food item.

Risks, Inconveniences and Discomforts

Medical history and Physical Exam:
There is minimal medical risk from these procedures.

Blood work:
You may feel some pain and discomfort at the needle entry site where blood is drawn or where the intravenous line is inserted. There is a slight risk of bleeding or bruising around the site. Some people feel lightheaded or dizzy. There is a remote risk of fainting and infection after having blood drawn. To reduce the risk of injury because of a fall, you will be closely monitored and asked about these symptoms before you are allowed to stand up. Clean aseptic technique will be used by experience staff while drawing your blood. A total of about 556 ml (about 2.4 cups) of blood will be taken over the entire study.

Genetic testing -DNA analysis:

The DNA analysis (APOE genotyping and DNA Methylation studies) that will be done as part of this study is done for research purposes only. There may be no direct personal benefit to you from participating in this study, but you will be contributing to the effort to better understand the genetic disorder, which may improve the lives of others with this condition in the future.

Genetic testing can provide information about how health or illness is passed on within your family. This knowledge may affect your emotional wellbeing. You might feel differently about your life if you learned that you or your children were at increased risk of a disease, especially if there were no treatments. This is the case of the APOE ε4 gene, for which we test in this study and which increases the risk of Alzheimer's disease and heart disease, although it does not mean that whomever carries that gene will develop Alzheimer's disease or heart disease.

Your children, brothers or sisters may find out that they are at risk for health problems because of information found out about you, which might affect your relationships with them. Other family members may also be affected by uncovering risks they have but did not want to know about. This information can cause stress, anxiety, or depression.

Because of the emotional risk, some people who participate in research do not want to know the results of genetic testing. It is our policy to not disclose the results of genetic testing unless it may have direct medical or reproductive implications for you or your family. You may choose to receive your information, or you may choose not to receive the information. Whether you choose to receive the information or not, by agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, you can contact the principal investigator of this study

Results of genetic testing obtained at NIH are often preliminary and difficult to interpret because the testing is being done for research purposes only and the laboratories are not clinically certified. You may be referred to another laboratory for clinical testing or confirmation. This is the case of the testing for the APOE ε4 gene that will take place in this study. In addition, testing for the APOE ε4 gene may take place after the end of your study participation and may not be immediately available for review. If you decide that you want to know the results of APOE ε4 gene testing as performed in this study, you will meet with the principal investigator to discuss the results. You will be referred to a clinically-certified laboratory to repeat the testing and confirm the results; the NIA will not cover the cost associated with repeating the genetic testing for APOE ε4. The principal investigator will discuss with you the significance of the results regarding the risk of developing Alzheimer's disease and heart disease for you and your family. In addition, genetic counseling is available at the National Institutes of Health to help you understand the nature and implications of you and your family's genetic findings.

Your genetic information will be kept confidential to the extent possible. The results of your genetic testing will be kept in a locked and secured manner at the NIH. Genetic information will not be part of your medical record. Genetic information about you will not be revealed to others, including your relatives, without your written permission. Similarly, you will not receive information about other family members.

Problems, such as with insurance or employment discrimination, may occur if you disclose information about yourself or agree to have your research records released. We will not release any information about you or your family to any physician, insurance company or employer unless you sign a document allowing release of the information.

Urine testing
There are minimal risks for providing a urine sample.

Urine Pregnancy testing:
There is minimal risk to giving a urine sample for pregnancy testing. However, due to the potential risk of MRI and fluoroscopic LP on pregnancy or fetal development, if you are a woman who is able to become pregnant, you will have a pregnancy test done before these procedures. You will not be able to participate in the study if your pregnancy test is positive.

Lumbar puncture (or spinal tap):
You may experience a brief pain or tingling sensation in your legs during the procedure if the needle brushes against a nerve. If this happens, please let the doctor know immediately and the needle will be adjusted. Following a lumbar puncture, some people have a mild backache at the site of needle insertion. About one-third of people have a headache for a few days after a lumbar puncture. Usually the headache is not severe and improves without treatment other than

a mild pain reliever. Headaches lasting longer than 7 days develop with one in 50 to 200 lumbar punctures and usually improve gradually over 2 weeks. In rare cases, headaches have persisted longer. Prolonged headaches may be due to persistent leakage of cerebral spinal fluid (CSF) from the area of the lumbar puncture. If your headache is prolonged, you and your doctor may decide to perform a "blood patch." A blood patch requires removing blood with a needle from a vein in your arm and then injecting it into the area of your back where the lumbar puncture was performed to seal off the leak of CSF. Bleeding in the spinal cord or brain is a very rare complication. To help prevent this rare complication, we will draw blood on you before the procedure to assess your body's ability to clot. If you are found to have abnormal values on these tests, you will not have a lumbar puncture performed.

Radiation exposure (only if lumbar puncture requires x-ray guidance)

If the lumbar puncture (LP) procedure is considered technically difficult by the physician, or we are not able to obtain the spinal fluid sample at the bedside, a licensed radiologist may perform the procedure under x-ray guidance.

This radiation exposure is not required for your medical care and is for research purposes only. This research study may involve exposure to radiation from up to three lumbar punctures. The amount of radiation you may receive in this study is up to 0.74 rem, which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space and from radioactive materials that are found naturally in the earth's air and soil.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. Please tell the study staff if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy, as well as nuclear medicine scans in which radioactive materials were injected into your body.

3-hour mixed meal tolerance test (MMTT)

You may experience a sense of abdominal fullness or discomfort, nausea, vomiting, or diarrhea, but it is a rare occurrence.

5-2 CR diet

You may find that the provided Boost® shakes may not be what you prefer to eat, and that it is a challenge to follow the diet. Additionally, you will not be able to eat any other food on the two days that you choose to drink the meal replacement shake. This may be an inconvenience. Some people have experienced hunger, headaches, feeling cold, constipated, lack of concentration, bad temper and a preoccupation with food. These effects stopped after stopping the diet.

"Healthy living" diet
You may not be used to eating a healthy and balanced diet with fruits, vegetables and low fat. This may be an inconvenience. Some people may experience cravings for unhealthy foods/snacks, bad temper and preoccupation with food.

Physical activity monitor - Accelerometer
There are minimal risks for wearing this device. It may be inconvenient to wear and to write your activities on the form (diary) provided.

Study questionnaires
Completing the questionnaires may be time-consuming and inconvenient.

Cognitive tests
The tests are not harmful but may be frustrating or stressful. We only ask that you do your best. No one performs perfectly on these tasks. If you get tired you can ask for a break. You may choose not to answer every question, or you may choose to stop testing all together. These tests will take about 1 hour to complete.

Magnetic Resonance Imaging (MRI scan)
People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these conditions before having any scan, and if you have any, you will not receive an MRI scan. If you have a question about any metal objects being present in your body, you should inform the staff. In addition, all magnetic objects (for example, watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

Rarely, you may feel a vibration or tingling of your skin during the MRI due to the magnetic fields. These sensations will stop when the MRI is stopped. Please let the MRI technician know if you have these, or any other sensations and the MRI will be stopped at your request. Because each MRI is different, participation in future MRIs will depend on the type of MRI that is requested and your previous response.

It is not known if MRI is completely safe for a developing fetus. The scan will not be done if pregnancy tests are positive.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing

protection comes loose during the scan, you should let us know right away. Please notify the investigator if you have hearing or ear problems. You will be asked to complete an MRI screening form for each MRI scan you have. There are no known long-term risks of MRI scans.

Incidental findings (brain MRI scan)
A potential risk of participating in this study is that the radiologist who reviews brain images may find a brain abnormality of uncertain significance. We will inform you about any finding that may require further evaluation or care. We are not able to provide evaluation or treatment for these conditions at NIH. If needed, we will refer you to a health care provider. We may not inform you about minor abnormalities that do not have importance for your health or well-being.

Research Use and Disposition of Human Samples and Data

The NIA will retain custody of your samples and data for studies as outlined above. The NIA will be the exclusive owner of any data, discoveries or derivative materials from the sample materials and is responsible for the restriction of sample use at your request. If a potential commercial product is developed from the research project, the NIA will develop patents and promote commercialization of the product as required by law. You will not profit financially from such a product.

Your samples will be stored in secured freezers at the NIA facility. Your name and identifying information will be removed and we will assign the sample a code. The key to the code will be kept in a separate, secure area. At the completion of this study your data and samples will be put into the NIA Sample and Data Repository Protocol. Your samples will be used only for the study described in this consent form, unless you give us permission to use them for other studies, including studies not related to how the brain responds to insulin or Alzheimer's disease. Please initial on the line below reflecting how you would like your samples used:

_____ YES. You may use my samples used for other research projects, including those not related to how the brain responds to insulin or Alzheimer's disease

_____ NO. I do not want my samples used for other research projects. Please destroy my samples once this project is complete

If you allow future research on your samples and the research provides information important for your health, we will try to contact you. If you wish to be contacted please keep the principal investigator for this study or the NIA updated about changes in your address or phone number.

If you allow future research on your samples, we may share them with collaborating laboratories at NIH or outside of NIH. We may share blood and cerebrospinal fluid samples, MRI images, MRS data, cognitive test results, and data from the DNA analysis. Prior to sharing, we will either strip any personal identifiers and code them ("de-identified") or unlink them from any identifying code ("anonymized"). When coded "de-identified" data or samples are shared, the key to the code will not be provided to collaborators, but will remain at NIH.

Anticipated Benefits

There is no direct benefit from participating in this research study; however, we hope to learn more about how different diets can lower insulin resistance and improve genetic markers associated with Alzheimer.

Right of Withdrawal and Conditions for Early Withdrawal

You may withdraw from the study at any time and for any reason without loss of benefits or privileges to which you are otherwise entitled. The investigator can remove you from the study at any time of he or she believes that continuation is not in your best medical interest or if you are unable to comply with the requirements of the study.

Results from this Study

You may receive some baseline evaluations (blood work) during the study that may give you information about your health. All other procedures that we do and the results that we obtain in this study are for research purposes only. We will share with you any new information that may relate to your willingness to continue to participate in this study.

Study Termination

You may be removed from the study if:

- You develop a new medical condition that is listed in the exclusion criteria
- You are unable or unwilling to comply with the study requirements
- You lose more than 5% of your body weight within 2 weeks on two separate two-week visits
- The study physician, Dr. Dimitrios Kapogiannis, deems it unsafe for you to remain in the study
- The study is stopped

Alternatives to Participation or Treatment

- The alternative to participating in this study is not to participate
- You have the option to follow a standard diet and exercise of your own free will
- You have the option to receive health care, such as weight management or medications to improve your blood glucose from your primary care provider

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

The amount of compensation is guided by NIH policies and guidelines. You will be compensated for research-related discomfort and inconveniences. The total possible compensation for this study is about 1,350 dollars. You will receive payment on a debit card. Accommodations may also be provided if an overnight stay is necessary.

Screening	$50
Baseline	$350
Week # 2 Visit	$150
Week # 4 Visit	$150
Week # 6 Visit	$150
Week # 8 Visit	$500

If you are unable to finish the study, you will be paid for the parts you completed.

Blood draw	$20
Mixed Meal Test (MMTT)	$50
MRI	$50
Lumbar Puncture LP	$150
Cognitive Testing	$20
Physical Activity Monitor	$40 ($10/day to wear)
Calorie restriction per week	$50

You will receive a meal ticket for visits that require fasting.

This study does not offer reimbursement for travel, or lodging.

With few exceptions, study compensation is considered taxable income that is reportable to the Internal Review Service (IRS). A “Form 1099-Other Income” will be sent to you if your total payments for research participation are $600 or more in a calendar year. If you have unpaid debt to the federal government, please be aware that some or all of your compensation may be automatically reduced to repay that debt on your behalf.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH.

Conflict of Interest

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

NIA will provide short-term medical care for any physical injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, NIA, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dimitrios Kapogiannis, M.D. at kapogiannisd@mail.nih.gov or 410-350-3953. You may also call the Clinical Director at (410) 350-3922; the NIA Clinical Research Protocol Office at (410) 350-3947, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.