COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2016-2)
YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL
(Age range 18-25 years)

Study Title: Mechanisms of Obesity and Its Metabolic Complications in Youth
Principal Investigator: *Nicola Santoro*
Funding Source: *National Institute of Health*

ADULT CONSENT: 18 Years and older

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at the mechanisms leading to pediatric obesity. You have been asked to take part because your BMI is greater than 95th percentile or because you are at risk for obesity and diabetes due to a family history but you are lean. The study aims at enrolling 200 participants.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Several data in the literature suggest that the composition of the intestinal flora (the bugs present in the gut) might influence fat accumulation and lead to obesity and that this might happen through a higher formation in the intestine of certain compounds (namely short chain fatty acids) that are converted into fat and accumulated in the human body as such.

Therefore, the goal of our study is to find out whether young subjects who are overweight or obese experience a higher formation of these compounds, short chain fatty acids (SCFA) and a higher conversion of SCFA in fat (through the hepatic lipogenesis) than subjects who are not overweight or obese.

If you agree to take part in this study, you will be asked to undergo the following procedures:

You will be instructed about the benefit of a healthy diet and will meet with the dietician who will advise on healthy feeding behavior and lifestyle. If you decide to participate in more than part (aim) of the study, your visits will be scheduled at least 12 weeks apart.

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Screening visit. Before the enrollment, your eligibility will be assessed through a clinical evaluation during a screening visit in which the PI will assess the eligibility through a comprehensive physical examination and blood testing.

Hematocrit (Hct) measurement; To assess whether it is safe to perform the study we will measure the hematocrit (HcT), an indirect measure of anemia. Before the study, a small blood draw will be taken prior to participation to evaluate the Hct levels. If the Hct level is found to be lower than 32% than the visit will be re-scheduled.

1) Measurement of the synthesis of short chain fatty acids

To reach our goal we would like to measure the SCFA using acetate labeled with deuterium and lactulose. Acetate and lactulose are a compounds widely diffuse in nature. Inulin is not absorbed as such, but is converted by the gut bacteria in SCFA such as Acetate. Acetate is used by the liver also to synthetize fat. These are two naturally occurring compounds usually found in fruit and vegetables (such as chicory). In particular we would ask you to arrive to the Hospital Research Unit of the Yale New Haven Hospital at 7am, having fasted from 08:00 PM the night prior, and drink 0.7 micromol/Kg/min of labeled acetate after a priming of 15 micromol/Kg in 4 minutes and ask to take 20 grams of lactulose diluted in 200 mL of water. We will draw blood at beginning of the study and then every hour until the end of the study. A thin plastic tube (I.V.) will be placed in a vein. We will draw 150 ml of blood to measure SCFA formation, this is the equivalent of about 3 and half tablespoons. The study will last until 6.00 PM. You will be allowed to drink water during the study and a meal will be served at the end. **Diet standardization before the study.** Before the study our dietician will instruct you on how to eat for three days before the study. During this period, we would like you to maintain constant your caloric intake. We will also collect the breath hourly during the study to assess colonic fermentation by measuring hydrogen in the breath.

Part 1: Follow-up: After the completion of part 1 of this study, you will be invited back for a one-year follow-up to measure height, weight, body mass composition with the Tanita scale, and to collect a 3-day food log. This part is simple and non-invasive.

2) Diet Intervention (subset of the subjects who complete *Measurement of the synthesis of short chain fatty acids*)

A subset of the subjects who complete the measurement of the formation of short chain fatty acids will be asked to participate in the diet intervention study and follow low carbohydrate diet and a standard diet. The two interventions (low and standard carbohydrates diet) will be separated by an interval of 4 weeks of regular eating period. The diet will last for 7 days and the food will be provided by the Metabolic Kitchen of the Yale New Haven Hospital. Before starting the diet, you and you will be instructed by a Registered Dietician on the benefits of the diet and on its composition and will be asked to try it for a couple of days. If you think to be able to follow this diet for 7 days, then you will be enrolled in this branch of the study.

3) Repeated Measurement of the synthesis of short chain fatty acids post *Diet Intervention*

Since we would like to prove the effect of a low carbohydrates diet on the formation of the SCFA in the intestine, we will ask you to repeat the *Measurement of the synthesis of short chain fatty acids* **after**

completion of the *Diet Interventions*. In particular, we would ask you to arrive to the Hospital Research Unit of the Yale New Haven Hospital at 7am, having fasted from 08:00 PM the night prior, and will infuse 0.7 micromol/Kg/min of labeled acetate after dose of 1 mg/kg for 4 minutes and ask to take 20 grams of lactulose diluted in 200 mL of water. We will draw blood at beginning of the study and then every hour until the end of the study. A thin plastic tube (I.V.) will be placed in a vein. We will draw 150 ml of blood to measure SCFA formation, this is the equivalent of about 9 and half tablespoons each draw. The study will last until 6.00 PM. You will be allowed to drink water during the study and a meal will be served at the end. We will also collect the breath hourly during the study to assess colonic fermentation by measuring hydrogen in the breath.

4) Measurement of the synthesis of intra-hepatic fat synthesis

We would like to assess whether the products of the microbial metabolism are converted in fat. For this visit, you will be asked to drink some deuterium, a naturally occurring compound known also as heavy water (3 cups) the night before the study. We will provide the heavy water and you will need to drink it the evening before the study. In particular, the administration needs to occur at 7:00 PM, 9:00 PM and 3:00 AM. Then you will be admitted to the HRU at 7.30am the following day and will be asked to ingest 15 grams of inulin (of those 2g are labeled with 13C). Inulin is a carbohydrate that is naturally found in the vegetable chicory root. We are using this type of carbohydrate because it tends to bypass primary digestion and is digested by the gut bacteria instead. We will draw 150 ml of blood (about 9 and half tablespoons) during the study that will last until 8 PM. You will be allowed to drink water during the study and a meal will be served at the end. We will also collect the breath hourly during the study to assess colonic fermentation by measuring hydrogen in the breath.

5) Assessment of glucose tolerance and measurement of liver fat

<u>Oral Glucose Tolerance Test.</u>

Prior to coming in for the oral glucose tolerance test (OGTT), you will be given a diet plan that you need to follow the day before the OGTT. We also ask that you refrain from strenuous exercise the day before the OGTT. This will help us to obtain more reliable information from the test.

The test will be done within the Yale Center for Clinician Investigation of Yale-New Haven Hospital. The duration of the test is about four hours. At the beginning of the test, we will obtain a family and medical history, and we will measure your height, weight, waist circumference, hip circumference, pulse, and blood pressure. We will examine your skin for stretch marks and for acanthosis nigricans, which is a change in the color and roughness of the skin that is often found on the back of the neck and in the armpits of individuals with high insulin levels. We may also look for changes that take place at puberty. In addition, we will ask you for a urine sample, which will be used to find out if you have tiny amounts of a protein called albumin in your urine.

A thin plastic tube (I.V.) will be placed in a vein in your arm. You will then be asked to drink about 8 ounces (one cup) of a high-sugar cola- or orange-flavored drink. The I.V., which will remain in place for the duration of the test, will allow a member of the research team to take out small amounts of blood for measuring the concentration of glucose and other substances that circulate in the blood. A total of

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120 ml (8 tablespoons) of blood will be drawn. A television and VCR are available to watch. Lunch will be provided at the end of the test.

Belly Scan (MRI)

We will measure how much fat is in your belly using techniques called magnetic resonance imaging (MRI). This method is painless and is thought to be very safe. You will be asked to complete a safety questionnaire, and we will ask you to remove any loose metallic items, such as watches, jewelry and hairclips.

Magnetic Resonance Imaging (MRI) will be used to take pictures of your belly. These pictures will allow us to calculate how much fat you have just below the skin and how much fat is deeper inside the belly. We will also be able to estimate the percentage of fat in your liver and how much iron is in your liver. You will be asked to lie down on a movable platform that slides into a hollow cylinder-shaped scanner. A belt will be placed around your belly, near the bottom of the ribcage. This belt allows the scanner to know when you are breathing in and out, which helps reduce blurring of the pictures caused by breathing. We will also place a thin rectangular-shaped coil across your belly. This will allow us to get better pictures of the liver. Other than slight vibrations, you will feel no unusual sensations. However, the magnet will make a loud buzzing noise when it is taking pictures. You will be given protective headphones or earplugs to wear so the noise won't be too loud. The scanner will take several pictures of the belly. The MRI operator will tell you when each scan will be performed. It is important that you lie still at this time. If any of the pictures do not develop correctly, we may need to repeat them. For most of the scans, you will just need to lie still. However, toward the end, there will be a few pictures where you will be asked to hold your breath for about 15 to 30 seconds each time. The MRI operator will go through some breathing exercises with you and will tell you exactly when to hold your breath. You will be allowed to catch your breath between pictures. If any of the pictures are blurred or do not develop correctly, you may be asked to repeat this picture by holding your breath once more. You will be able to be heard by the MRI operator during the scan, and the operator will be able to talk to you through a microphone when necessary. The entire scan should take no more than 30 minutes. If you want to get out of the magnet at any time, for any reason, we will take you out right away.

6) Measurement of the synthesis of glucose (gluconeogenesis)

We would like to assess whether the products of the microbial metabolism can influence the ability of the body to make glucose. For this visit, you will be asked to drink some deuterium, a naturally occurring compound known also as heavy water (3 cups) the night before the study. We will provide the heavy water and you will need to drink it the evening before the study at about 7:00 PM, 9:00 PM and 3:00 AM. Then you will be admitted to the research unit at 7:30am the following day and will be asked to ingest 20 grams of lactulose. We are using lactulose because it tends to bypass primary digestion and is digested by the gut bacteria instead. We will draw blood at beginning of the study and then every hour until the end of the study via IV in a vein. We will draw 150 ml of blood (equivalent of about 9 and half table spoons) that will last until 8 PM. You will be allowed to drink during the study, a meal will be served at the end of the study. We will also collect the breath hourly during the study to assess colonic fermentation by measuring hydrogen in the breath.

7) Assessment of dietary changes post COVID-19 lockdown

Since the initiation of COVID-19 lockdown, many youth have been at home. Because of this change in everyday lifestyle, we would like to assess how the lockdown has influenced your dietary habits. In order to collect this information, we will ask you to complete an online 3-day food record. This part of the study is non-invasive and there will be no in-person contact.

8) Measurement of TCA cycle in the brain and in the liver by using Deuterium metabolic imaging.

We would like to assess the synthesis of compounds involved in TCA cycle in brain and liver. We will use a technique that combines stable isotopes and MRI for this assessment. Deuterium metabolic imaging (DMI) is a simple MR-based technique to map metabolism with high temporal and/or spatial resolution. The metabolic fate of deuterated substrates, including glucose and acetate, can be monitored with deuterium MR methods.
This visit will take place in Yale Magnetic Resonance Research Center (MRRC).

TCA cycle measurement in the brain.
To measure TCA cycle measurement in the brain we will infuse 6,6-2H2-glucose for 2 hours and we will detect the changes in TCA derived compounds in the brain during the infusion. A total of 50 ml of blood will be obtained during this study. The labeled glucose is prepared by the Investigational Drug Service of the Yale Pharmacy, as a solution of 20% (w/v) in water. The labeled glucose is infused following a protocol used for decades in the Yale Magnetic Resonance Research Center (MRRC), consisting of a ramp phase followed by a plateau phase. The amount of glucose infused is 0.75g/kg body weight (BW); the volume of glucose solution infused over a 120 min study is 3.6 ml/kg BW.

TCA cycle measurement in the liver.
To measure TCA cycle measurement in the liver we will infuse d3-acetate for 2 hours and we will detect the changes in TCA derived compounds in the liver during the infusion. A total of 50 ml of blood will be obtained during this study. The labeled acetate is prepared by the Investigational Drug Service of the Yale Pharmacy, as a solution of 350 mM 2H-labeled sodium-acetate in water. The labeled acetate is infused following a protocol used for decades in the Yale MRRC, consisting of a ramp phase followed by a plateau phase. The amount of acetate infused is 0.73g/kg body weight (BW); the volume of acetate solution infused over a 120 min study is 14.2 ml/kg BW.

Why use labeled water and inulin? We will ask you to drink labeled water so that we can measure the creation of fatty acids in the liver and the gut. The labeled water that we use is called “heavy water” and is the same as normal water, except the hydrogen in H_2O has an extra neutron. This “labeled molecule” will be incorporated in the newly formed fatty acids during their synthesis and allow us to track fats being made in your body. We will ask you to drink inulin because it is a carbohydrate that bypasses primary digestion and will be digested by your gut bacteria. This way, we know that the fats being made from digestion are truly coming from the gut bacteria.

Other procedures:

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Tanita
We may ask you to step onto a Tanita scale, which is a special scale that delivers a very mild electrical current that you won't be able to feel. This will allow us to measure the amount of fat and muscle in your body.

Stool Sample
You will be asked to provide stool samples which will be obtained either during any of the tests you complete as part of this study or completed at home and returned. We will provide you with a kit to collect the sample. Within this kit is a cover for the toilet seat, a container and lid for the specimen, a cooler, cooler packs, and a plastic bag. You will need to put the cooler packs in the freezer as soon as you receive them. You will collect the sample using the toilet seat cover and container, place inside a box with the provided frozen ice packs and bring back to Yale within 12 hours.

Pregnancy test
We will ask you to have a pregnancy test before you start this study. You will be asked not to be in the study or you will be removed from the study if your pregnancy test is positive.

Risks and Inconveniences
These studies involve the placement of an I.V. in a vein in your hand or arm, which can cause a bruise or discomfort. Rarely, infection, a blood clot, inflammation, or bleeding can occur at the site. If pain is a concern, we can use a special numbing medicine that will minimize the pain. If inflammation of the vein (also called phlebitis) does occur, application of a warm soak to the site and elevation of the arm will help. Very rarely, someone may faint, or more likely become lightheaded or nauseated, when the I.V. is put in. You may be given Tylenol if needed. All I.V.s will be placed and removed while you are sitting or lying in bed in case dizziness does occur. The Hospital Research Unit nurses who put in the I.V.s has special training and experience in drawing blood. This should help keep the risks at the very lowest level possible. Your blood pressure and heart rate will be checked at the beginning of the infusion studies to ensure that you are stable. The nurse will then assess you throughout the study.

Since lactulose and inulin are not absorbed, it may cause uncomfortable bowel movements, flatulence, loose stools, bloating, cramps, and diarrhea. The risk of using compounds such as Acetate, Deuterium, and inulin appears to be negligible. In fact, these compounds will be given orally, therefore there will not be any risk related to sterility and infections. The risk of acetate infusion use is minor. Acetate is largely present in our body. Labeled acetate has been used for years in medical research over the world including Yale (Petersen KF Cell Metabolism 2016) without any side effects. Infusion is via existing IV. The dose of D20 used in this study are in the range of 1-2 mg/Kg of weight, which is what is commonly used in clinical studies. Also, in the past infusions of these compounds have been used to evaluate the SCFA turnover in newborns without any side effect. The risk of using glucose also appears to be negligible. Glucose is naturally occurring in our body. The labeled glucose has been used for many years in clinical studies.

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. You will be watched closely throughout the MR study. Some people

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may feel uncomfortable or anxious. If this happens to you, you may ask to stop the study at any time and we will take you out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but please tell the research staff if you have them.

There are some risks with an MR study for certain people. If you have a pacemaker or some metal objects inside your body, you may not be in this study because the strong magnets in the MR scanner might harm you. Another risk is the possibility of metal objects being pulled into the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. It is important to know that no metal can be brought into the magnet room at any time. Also, once you are in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information you think might be important. This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on your scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact you, inform you of the finding, and recommend that you seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with you and your physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that you receive based on these findings. The images collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

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.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.

Benefits

You may learn more about healthy behavior and the quality of food that you consume every day. In fact, all the subjects will be instructed about the benefit of a healthy diet and will meet with the dietician who will advise on healthy feeding behavior and lifestyle. This may help you to developing a healthier feeding behavior and to improve your metabolic (plasma glucose, lipids etc.) outcomes. If you decide to be enrolled in the diet study, you will undergo a low carbohydrates diet for a week. The food will be provided to you and there will be no cost on your side. Otherwise, the benefits to the general population and to science are the improvement in the knowledge of the pathogenesis (the overall development of) obesity.

Alternatives

You do not need to take part in this research study to seek care for overweight or obesity. You will be given the chance to attend the Yale pediatric Obesity Clinic available at the Department of Pediatrics of Yale University regardless of their decision to participate in the study

Economic Considerations

You will not be charged for any research-related procedures or blood tests. You will receive $150 for every study, $150 for each MRI/Infusion study, $60 for the MRI, $50 for the glucose test, $20 for completion of a 3-day food log, and $20 for an at home stool collection. We will pay for parking.

We will use a pre-paid debit card to provide payment for taking part in the study. We will have to share your name, address, and telephone number with the banking institution issuing the debit card for ePayments. You may receive a card in the mail with the first payment following completion of the first visit. You will need to activate the card over the phone. Payments for additional visits will be automatically added to your card after completion of each following visit. You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments."

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income.

Should you withdraw from the study for any reason after it has begun, you will be paid for that portion of the study in which you have participated.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a person, or certain reportable diseases.

Data will be stored on password-protected computers, which are accessible only to members of our research team and those involved in managing our secure on-line database. In particular, the data will be stored in OnCore that is a Yale's Clinical Trials Management System (CTMS).

According to Yale policy the data will be stored in encrypted computers. Blood samples will be labeled with your initials and medical record number and will be stored in laboratories that are locked when not in use. If research blood is sent to outside laboratories for analysis, the samples will be de-identified, and the code will be stored on password-protected computers accessible only to members of the research team. Data from these studies may be shared between members of our research group. When the results of the research are published, or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.
In addition, you need to know that if you have ever been a patient at YNHH at any time, your previous medical records of other visits or admissions will become available to the researchers and to the staff of

the HRU when information from these visits or admissions is added into the medical record and if you do not have a medical record, one will be created.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and medical record number. The principal investigator will keep a link that identifies you to your coded information, but this link will be kept secure and available only to the PI or selected members of the research team. For subjects who opt not to store their data long term, data will be anonymized within three years after the end of the study.

The information about your health that will be collected in this study includes

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The following information:
    - Records about phone calls made as part of this research
    - Records about your study visits
    - Information obtained during this research regarding
    - Physical exams
    - Diaries and questionnaires

Information about your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Health care providers who provide services to you in connection with this study
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) called the Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for insuring research compliance. These individuals are required to keep all information confidential.
- The Principal Investigator: Dr. Nicola Santoro, co-investigators, and research staff
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: The Yale Human Investigation Committee (HIC), Yale Center for Clinical Investigation
- Others: Authorized representatives of the Food and Drug Administration (FDA) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

By signing this research authorization form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to that research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability

Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information; agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Representatives from the Yale Human Investigation Committee and the National Institutes of Health (the study sponsor) may inspect study records during internal auditing procedures. You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by [The National Institute of Health] which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document including research data in the medical record.

In Case of Injury

In the event that you are injured from being in the study, we will take care of your injuries. However, you or your insurance carrier will be billed for the cost of that treatment. No additional financial compensation is available. You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. This might occur because of non-compliance with appointments or if medications were started that exclude you, for example.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Pediatric Endocrinology.

Withdrawing Your Authorization to Use and Disclose Your Health Information

You may withdraw or take away your permission to use and disclose your health information at any time. You may withdraw your permission by telling the study staff or by writing to Dr. Nicola Santoro at Yale University P.O.Box 208064, New Haven, CT 06520 or nicola.santoro@yale.edu.

If you withdraw your permission, you will not be able to stay in this study.
When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions.

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Optional Specimens for Future Storage

You are invited to allow some of your blood samples (called specimens) and related information collected in this study to be stored (banked) for future research. This may help researchers in the future learn more about how to prevent, find and treat obesity. The samples will be stored long term in the facilities of the Core laboratories of the Yale Center for Clinical Investigation.

When your specimens and information are stored, we are careful to try to protect your identity from discovery by others. Your samples and information will receive a unique code. Other researchers

will only receive coded samples and information, and will not be able to link the code to you. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.

Using your specimens for research will probably not help you. We do hope the research results will help people in the future. Your specimens and information will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you. Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

The choice to take part is up to you. You may choose not to let us store and use your samples,

Name of Subject:_____

Signature:_____

Date:_____

_____ _____

and your care will not be affected by this decision. If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff by phone or mail to let them know you do not want your samples used any longer. Your samples will either be destroyed, or made anonymous (the code linking them to you will be destroyed).

I agree to allow my samples and information to be stored and used for future research as described above: (initial your choice)

_____YES _____No

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

By signing this form, I give permission to the researchers to use [and give out] information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator Nicola Santoro 203-737-6356. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.