STUDY INFORMED CONSENT

Official Title Genetic-specific effects of fructose on liver lipogenesis

NCT number NCT03783195

Document Date 03/09/2021

University of North Carolina at Chapel Hill
Consent to Participate in a Research Study
Adult Participants

Consent Form Version Date: 03/09/2021
IRB Study # 17-3348
Title of Study: Fructose-liver fat study
Principal Investigator: Saroja Voruganti
Principal Investigator Department: Nutrition Operations
Principal Investigator Phone number: 704-250-5009
Principal Investigator Email Address: saroja@email.unc.edu

Concise Summary
This study proposes to find whether a set of genetic markers will increase the risk of fatty liver in children and adults between the ages of 12 and 40years when consuming two fructose drinks per day. At the start of the study and at the end of three weeks, participants will have their liver imaged by MRI, provide body weight, height, fat and blood biomarkers and have ultrasound conducted for their liver. They will also provide blood and urine at baseline, 1 hour and 3 hours after drinking the sugar drinks at week 0 and week 3. For females, a pregnancy test will be conducted on day 1 of phases 2 and 3. If pregnant, they cannot continue in the study. Similarly, if the liver fat is found to be higher than normal during MRI in phase 2, they will not continue in the study. Risks include potential for weight gain. Blood draws and sugar drinks can also cause dizziness and a feeling of nausea in some cases.

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary.
You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this research study is to determine whether fructose increases liver fat and whether this increase is dependent on individual's genetic make-up. Fructose is a type of sugar found in plants and foods such as sugar cane, honey, berries, and root vegetables. This study will help us identify individuals who are at higher risk for fat accumulation in the liver leading to fatty liver and hepatitis not caused by excessive alcohol intake.

You are being asked to be in the study because you are Caucasian and between 18 and 40 years of age.

Are there any reasons you should not be in this study
You should not be in this study if you are not Caucasian, not between ages 18 and 40 years, have a history of alcohol

abuse, drink more than 14 sugar drinks per week or drink none at all, have diabetes or pre-diabetes, have adverse reaction to fructose or any sugar consumption, or have liver or kidney disease.

How many people will take part in this study?
This study will consist of three phases. There will be approximately 100 participants in phase 1 and 24 will be selected for phases 2 and 3.

How long will your part in this study last?
This study includes three phases: First phase is of 30-minute duration. You will be invited to take part in the second and third phase if you are selected based on your genetic makeup. The second and third phase will be of two days each, the first day being about 3 hours and the second day being 3.5 hours duration.

What will happen if you take part in the study?
Phase 1: You will be asked to provide informed consent, provide a saliva sample and fill out a short questionnaire including information related to your sugar intake. The saliva sample will be used to determine if you have a high or low genetic risk for fatty liver. If you do not have either a high or a low risk, you will not continue on to phase 2 of the study.

Phase 2: If you are one of the 24 selected participants,

Day 1: You will visit NRI from where study investigators will take you to the WakeForest Imaging center to scan your liver for fat accumulation. If you are a female, we will conduct a urine test to check if you are pregnant before going to the Imaging center. If you are pregnant, you will not be able to continue in the study. At the Imaging center, if your liver fat is found to be more than normal, then you will not continue with the study. Otherwise you will come back to NRI the next day for further steps.

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (fibroscan), blood pressure and pulse wave velocity measurements, 2) agree to have your blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and 4) complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of day 2, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws. Blood sampling will be conducted by a trained phlebotomist. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablepoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

You can decide to complete the questionnaires during the study visit, or you can take them home and mail them back to the investigators. You may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

Week1-Week3: You will be given three weeks supply of sugar drinks. Each sugar drink is equal to 2 sodas and needs to be taken once daily. You should not drink any other sugary drinks during the three weeks.

Phase3:

Day 1: You will visit NRI from where study investigators will take you to the WakeForest Imaging center to scan your liver for fat accumulation. If you are a female, we will conduct the urine test again to test for pregnancy. If you are pregnant, you will not be able to continue in the study.

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (fibroscan), blood pressure and pulse wave velocity measurements, and 2) complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of visit 1, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws. Blood sampling will be conducted by a trained phlebotomist. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablepoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

What are the possible benefits from being in this study?

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study.

What are the possible risks or discomforts involved from being in this study?

The only invasive procedure in this study is blood drawing but there is no alternate way to obtain this information. To make the blood draws more comfortable, an in-dwelling catheter can be placed in your arm. If you do not want a catheter, you will receive a needle stick for every blood draw but we will do our best to provide comfort during each blood draw. Blood draws can also cause dizziness and a feeling of nausea in some cases. Please let the investigators know whether you get sick during blood draws or if you react adversely to blood draws.

Because you will be consuming drinks equal to 2 cans of soda every day for 3 weeks, there is a possibility of weight gain.

If it is known, through the clinical examination, that you have risk for certain metabolic disease we will contact you in confidence and advise you to consult your physician. There may be uncommon or previously unknown risks. You should report any problems to the researcher.

If you choose not to be in the study, what other treatment options do you have?

You do not have to be in this research study in order to receive treatment. You will be advised to consult your regular healthcare provider in case needed.

What if we learn about new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Whenever imaging (MRI, CT, X-ray, etc.) is done, there is the chance of finding something unexpected. Unexpected findings can have clinical significance, or no clinical significance. Clinically significant means that the MRI shows a problem that may or require further follow up or treatment. The imaging studies in this study will be reviewed by a qualified radiologist. You will be informed of any findings of clinical significance that may be discovered during the imaging procedure.

There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The MRI we are using in this research study is not the same quality as a MRI that you may have as part of your health care. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

Will I receive any other clinical results?
If measurement of blood values reveals an abnormal value, you will be told and advised to consult your regular healthcare provider. Also, you will not be able to continue in the study if we find that you may have diabetes or if your liver fat is too high at baseline. We will provide you a report of our finding of MRI or other processes which you can show to your personal physician for further treatment.

How will information about you be protected?
All data will be strictly confidential and will be stored with the Principal Investigator (Dr. Saroja Voruganti). All information will be coded and only the coded and anonymized data will be available to co-investigators for analysis.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally.

What will happen if you are injured by this research?
You can withdraw from this study at any time, without penalty. You may not have adverse reaction by drinking 2 sodas/day for 3 weeks. But if you feel otherwise, stop immediately and inform us.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Will you receive anything for being in this study?
This study has 3 phases. You will receive $25 for taking part in the first part of the study. You will receive$150 for taking part in the second phase and $150 for the third phase of the study. If you participate but are unable to complete the acute challenge part of the study, you will receive $50 for your time and effort. If you complete the acute challenge but not the 3-week intervention the you will receive $100 for your time and effort. If you complete one week of the intervention, then you will receive $150 for your time and effort. However, no shows and cancellations will not receive any money.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or

to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

Who is sponsoring this study?
This study is funded by the National Institutes of Health (NIH). This means the research team is being paid by the NIH for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

What is a Certificate of Confidentiality?
This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

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 an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Signature of Research Participant Date

_____

Printed Name of Research Participant

_____ _____

Signature of Research Team Member Obtaining Consent Date

_____

Printed Name of Research Team Member Obtaining Consent

University of North Carolina at Chapel Hill
Assent to Participate in a Research Study
Adolescent Participants age 15-17 yrs

Consent Form Version Date: 03/09/2021
IRB Study # 17-3348
Title of Study: Fructose-liver fat Study
Principal Investigator: Saroja Voruganti
Principal Investigator Department: Nutrition Operations
Principal Investigator Phone number: 704-250-5009
Principal Investigator Email Address: saroja@email.unc.edu
Co-Investigators: Baba Mass, Brea Correll Nance

Concise Summary
This study proposes to find whether a set of genetic markers will increase the risk of fatty liver in children and adults between the ages of 12 and 40years when consuming two fructose drinks per day. At the start of the study and at the end of three weeks, participants will have their liver imaged by MRI, provide body weight, height, fat and blood biomarkers and have ultrasound conducted for their liver. They will also provide blood and urine at baseline, 1 hour and 3 hours after drinking the sugar drinks at week 0 and week 3. For females, a pregnancy test will be conducted on day 1 of phases 2 and 3. If pregnant, they cannot continue in the study. Similarly, if the liver fat is found to be higher than normal during MRI in phase 2, they will not continue in the study. Risks include potential for weight gain. Blood draws and sugar drinks can also cause dizziness and a feeling of nausea in some cases.

What are some general things you should know about research studies?
You are being asked to take part in a research study. Your parent, or guardian, needs to give permission for you to be in this study. You do not have to be in this study if you don't want to, even if your parent has already given permission. To join the study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher, your health care provider, or the University of North Carolina-Chapel Hill. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this research study is to identify genetic factors that increase the risk of fat accumulation in the liver based on consumption of sugar drinks.

Are there any reasons you should not be in this study?
You should not be in this study if you are not Caucasian, not between ages 12 and 19 years, have a history of alcohol abuse, drink more than 14 sugar drinks per week or drink none at all, have diabetes or pre-diabetes, have adverse reaction to fructose or any sugar consumption, or have liver or kidney disease.

How many people will take part in this study?
There will be approximately 100 children in this research study.

How long will your part in this study last?
This study includes three phases: First phase is of 30-minute duration. You will be invited to take part in the second and

third phase if you are selected based on your genetic makeup. The second and third phase will be of two days each, the first day being about 3 hours and the second day being 3.5 hours duration.

What will happen if you take part in the study?

Phase 1: You will be asked to provide informed consent, provide a saliva sample and fill out a short questionnaire including information related to your sugar intake. The saliva sample will be used to determine if you have a high or low genetic risk for fatty liver. If you do not have either a high or a low risk, you will not continue on to phase 2 of the study.

Phase 2: If you are one of the 24 selected adolescents,

Day 1: You will visit University of North Carolina Nutrition Research Institute (UNC-NRI) from where study investigators will take you to the Wake Forest Imaging center to scan your liver for fat accumulation. If your liver fat is more than normal, then you will not continue with the study. If you are female, we will also conduct urine pregnancy test. If you are pregnant, you will not continue with the study. Otherwise you will come back to NRI the next day for further steps.

If you are pregnant, we will tell your parents about your test results if: 1) you agree that we can share this information with them or, 2) you are pregnant and do not appear to understand the situation, or if you become very emotional or expresses the potential of harming yourself or you feel that are in potential harm from a partner or someone else due to the pregnancy

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (Fibroscan), blood pressure and pulse wave velocity measurements, agree to have your blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of day 2, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws.
Blood sampling will be conducted by a trained phlebotomist. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablespoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

You can decide to complete the questionnaires during the study visit, or you can take them home and mail them back to the investigators. You may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

Week1-Week3: Your child will be given three weeks supply of sugar drinks. Each sugar drink is equal to 2 sodas and needs to be taken once daily. Your child should not drink any other sugary drinks during the three weeks.

Phase3:

Day 1: You will visit University of North Carolina Nutrition Research Institute (UNC-NRI) from where study investigators will take you to the Wake Forest Imaging center to scan your liver for fat accumulation. If your liver fat is more than normal, then you will not continue with the study. If you are female, we will also conduct urine pregnancy test. If you are pregnant, you will not continue with the study. Otherwise you will come back to NRI the next day for further steps.

If you are pregnant, we will tell your parents about your test results if: 1) you agree that we can share this information with them or, 2) you are pregnant and do not appear to understand the situation, or if you become very emotional or expresses the potential of harming yourself or you feel that are in potential harm from a partner or someone else due to the pregnancy

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (Fibroscan), blood pressure and pulse wave velocity measurements, agree to have your blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of day 2, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws.
Blood sampling will be conducted by a trained phlebotomist. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablespoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

You can decide to complete the questionnaires during the study visit, or you can take them home and mail them back to the investigators. You may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study. However, the knowledge related to the genetic effects on prevalent metabolic diseases will help the community in finding new treatment options.

What are the possible risks or discomforts involved from being in this study?
The only invasive procedure in this study is blood drawing but there is no alternate way to obtain this information. To make the blood draws more comfortable, an in-dwelling catheter can be placed in your arm. If you do not want a catheter, you will receive a needle stick for every blood draw but we will do our best to provide comfort during each blood draw. Blood draws and sugar drinks can also cause dizziness and a feeling of nausea in some cases. Please let the investigators know whether you get sick during blood draws or if you react adversely to blood draws.

Because you will be consuming drinks equal to 2 cans of soda every day for 3 weeks, there is a possibility of weight gain.

What if we learn about new findings or information during the study?
You will be given any new information gained during the course of the study that might affect your willingness to continue to participate.

Whenever imaging (MRI, CT, X-ray, etc.) is done, there is the chance of finding something unexpected. Unexpected findings can have clinical significance, or no clinical significance. Clinically significant means that the MRI shows a problem that may or require further follow up or treatment. The imaging studies in this study will be reviewed by a qualified radiologist. You will be informed of any findings of clinical significance that may be discovered during the imaging procedure.

There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as problems with getting insurance or a job, or feeling worried about a finding for which no treatment is required or appropriate). The MRI we are using in this research study is not the same quality as a MRI that you may have as part of your health care. If you believe you are having symptoms that may require clinical imaging, you should contact your primary care physician.

Will I receive any other clinical results?
If measurement of blood values reveals an abnormal value, you will be told and advised to consult your regular healthcare provider. Also, you will not be able to continue in the study if we find that you may have diabetes or if your

liver fat is too high at baseline. We will provide you a report of our finding of MRI or other processes which you can show to your personal physician for further treatment.

How will information about you be protected?

All data will be strictly confidential and will be stored with the Principal Investigator (Dr. Saroja Voruganti). All information will be coded and only the coded and anonymized data will be available to co-investigators for analysis.

Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

What is a Certificate of Confidentiality?

This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

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 an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Will my genetic information be shared?

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

By signing this informed consent document, you agree that some of the information generated by participating in this study and/or a copy of the consent form may be included in your medical record and that this information may be viewed by other physicians or caregivers who provide healthcare services to you. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study. Additionally, the information may be shared with your medical insurance plan if the research services provided are billed to your insurance.

Under North Carolina law, researchers are required to report information about the abuse or neglect of a child or disabled adult to local or state authorities.

Under North Carolina law, confidentiality does not extend to certain communicable diseases, such as TB, HIV, hepatitis, or other illnesses that put others at risk. If the researchers become aware that subjects have such an illness, they are required to report it to state authorities.

Will you receive results from research involving your specimens?
Most research with your specimens is not expected to yield new information that would be meaningful to share with you personally. There are no plans to re-contact you or other subjects with information about research results. The use of your samples may result in commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped

Will you receive anything for being in this study?
This study has 3 phases. You will receive $25 for taking part in the first part of the study. You will receive $150 for taking part in the second phase and $150 for the third phase of the study. If you participate but are unable to complete the acute challenge part of the study, you will receive $50 for your time and effort. If you complete the acute challenge but not the 3-week intervention the you will receive $100 for your time and effort. If you complete one week of the intervention, then you will receive $150 for your time and effort. However, no shows and cancellations will not receive any money.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

Who is sponsoring this study?
This study is funded by the National Institutes of Health (NIH). This means the research team is being paid by the NIH for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form**.**

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Participant's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate in this research study.

_____ _____

Your signature if you agree to be in the study Date

_____

Printed name if you agree to be in the study

_____ _____

Signature of Research Team Member Obtaining Assent Date

_____

Printed Name of Research Team Member Obtaining Assent

University of North Carolina at Chapel Hill
Assent to Participate in a Research Study
Minor Subjects (7-14 yrs)

Consent Form Version Date: 03/09/2021
IRB Study # 17-3348
Title of Study: Fructose-liver fat study
Person in charge of study: Dr. Saroja Voruganti
Where they work at UNC-Chapel Hill: Nutrition Operations
Other people working on this study: Baba Mass, Brea Correll Nance

The people named above are doing a research study.

These are some things we want you to know about research studies:
Your parent needs to give permission for you to be in this study. You do not have to be in this study if you don't want to, even if your parent has already given permission. You may stop being in the study at any time. If you decide to stop, no one will be angry or upset with you. Sometimes good things happen to people who take part in studies, and sometimes things happen that they may not like. We will tell you more about these things below.

Why are they doing this research study?
The purpose of this research study is to identify genetic factors that increase the risk of fat buildup in the liver based on drinking of sugary drinks.

Why are you being asked to be in this research study?
We want your participation in the study so that we can find out what is the risk for you to increase fat buildup in the liver leading to fatty liver disease when you drink a lot of added sugars as in sodas and energy drinks.

How many people will take part in this study?
If you decide to be in this study, you will be one of about 100 children in this research study.

What will happen during this study?
Phase 1: You will be asked to provide permission to be in the study, provide a saliva sample and fill out a short questionnaire including information related to your sugar intake. The saliva sample will be used to determine if you have a high or low genetic risk for fatty liver. If you do not have either a high or a low risk, you will not continue on to phase 2 of the study.

Phase 2: If you are one of the 24 selected children,

Day 1: You will visit University of North Carolina Nutrition Research Institute (UNC-NRI) from where study investigators will take you to the Wake Forest Imaging center to scan your liver for fat accumulation. If your liver fat is more than normal, then you will not continue with the study. If you are female, we will conduct a urine test to check if you are pregnant. If you are pregnant, then you will not continue in the study. Otherwise you will come back to NRI the next day for further steps.

If you have started having your period, pregnancy testing is required for participation in this study. You can only be in the study if you are not pregnant. If you are 12 years old, we will tell your parents about your test results. If you are 13 or older, we will tell your parents about your test results if: 1) you agree that we can share this information with them or, 2) you are pregnant and do not appear to understand the situation, or if you become very emotional or expresses the potential of harming yourself or you feel that are in potential harm from a partner or someone else due to the pregnancy

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (Fibroscan), blood pressure and pulse wave velocity measurements, agree to have

your blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of day 2, we will collect blood which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws. Blood sampling will be conducted by a person trained to draw blood. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablespoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

You can decide to complete the questionnaires during the study visit, or you can take them home and mail them back to the investigators. You may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

Week 1-Week 3: You will be given three weeks supply of sugar drinks. Each sugar drink is equal to 2 sodas and needs to be taken once daily. You should not drink any other sugary drinks during the three weeks.

Phase 3:

Day 1: You will visit University of North Carolina Nutrition Research Institute (UNC-NRI) from where study investigators will take you to the Wake Forest Imaging center to scan your liver for fat accumulation. If your liver fat is more than normal, then you will not continue with the study. If you are female, we will conduct a urine test to check if you are pregnant. If you are pregnant, then you will not continue in the study. Otherwise you will come back to NRI the next day for further steps.

If you have started having your period, pregnancy testing is required for participation in this study. You can only be in the study if you are not pregnant. If you are 12 years old, we will tell your parents about your test results. If you are 13 or older, we will tell your parents about your test results if: 1) you agree that we can share this information with them or, 2) you are pregnant and do not appear to understand the situation, or if you become very emotional or expresses the potential of harming yourself or you feel that are in potential harm from a partner or someone else due to the pregnancy

Day 2: You will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (Fibroscan), blood pressure and pulse wave velocity measurements, agree to have your blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and complete questionnaires about your lifestyle, dietary patterns, and medical history.

You will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for you for the evening prior to your participation. On the morning of day of day 2, we will collect blood which means blood will be drawn through a needle three times during the study. However, if you do not want to be poked three times you can choose an in-dwelling catheter (flexible needle) to be placed in your arm for multiple blood draws. Blood sampling will be conducted by a person trained to draw blood. We will give you ~600ml sugar-sweetened beverage (about two 12 fl oz soda cans). You will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablespoons) of blood before you drink the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before you drink the beverage and then again at 1 hour and 3 hours later.

You can decide to complete the questionnaires during the study visit, or you can take them home and mail them back to the investigators. You may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

Who will be told the things we learn about you in this study?
We will not tell anyone what you tell us without your permission unless there is something that could be dangerous to you or someone else.

What are the good things that might happen?
Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study. However, the knowledge related to the genetic effects on prevalent liver and related diseases will help the community in finding new treatment options.

What are the bad things that might happen?
Sometimes things happen to people in research studies that may make them feel bad. These are called "risks." These are the risks of this study: The only invasive procedure in this study is blood drawing but there is no other way to obtain this information. If it is known, through the clinical examination, that you have risk for certain liver-related disease we will contact you in confidence and advise you to consult your physician. Blood draws and drinking sugar drinks may sometimes cause nausea and dizziness. There is also a chance that sugar drinks may increase your weight.

Not all of these things may happen to you. None of them may happen or things may happen that the researchers don't know about. You should report any problems to the researcher.

What if you or your parents don't want you to be in this study?
If you or your parents don't want you to be in this study, you are free to not participate in the study. At any point of time, you may decide to not to continue to participate on the study.

Will you receive anything for being in this study?
This study has 3 phases. You will receive $25 for taking part in the first phase of the study. You will receive $150 for taking part in the second phase and $150 for the third phase of the study. If you participate but are unable to complete the acute challenge part of the study, you will receive $50 for your time and effort. If you complete the acute challenge but not the 3-week intervention you will receive $100 for your time and effort. If you complete one week of the intervention, then you will receive $150 for your time and effort. However, no shows and cancellations will not receive any money.

Your name, address, and U.S. tax payer identification number (SSN or ITIN) are required to process payments and/or to report taxable income to the IRS. You must complete a W-9 (for U.S. persons) or W-8BEN and the Foreign Vendor Withholding Assessment with supporting documents (for non-resident aliens) in order to receive payment for participation.

If you do not provide your SSN or ITIN, or complete the appropriate documentation noted above, we cannot issue you a payment for participation. However, you may still choose to participate in this study.

Will it cost you anything to be in this study?
It will not cost you anything to be in this study.

Who is sponsoring this study?
This study is funded by the National Institutes of Health (NIH). This means the research team is being paid by the NIH for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What is a Certificate of Confidentiality?
This research is covered by a Certificate of Confidentiality. With this Certificate, the researchers 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 proceedings in the United States, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate cannot be used to refuse a request for information from personnel of a federal or state agency that is sponsoring the study for auditing or evaluation purposes or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law, such as mandatory reporting requirements for child abuse or neglect, disabled adult abuse or neglect, communicable diseases, injuries caused by suspected criminal violence, cancer diagnosis or benign brain or central nervous system tumors or other mandatory reporting requirement under applicable law. The Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

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 an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

Who should you ask if you have any questions?

If you have questions you should ask the people listed on the first page of this form. If you have other questions, complaints or concerns about your rights while you are in this research study you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

If you sign your name below, it means that you agree to take part in this research study.

_____ _____

Your signature if you agree to be in the study Date

_____

Printed name if you agree to be in the study

_____ _____

Signature of Research Team Member Obtaining Assent Date

_____

Printed Name of Research Team Member Obtaining Assent

University of North Carolina at Chapel Hill
Parental Permission for a Minor Child to Participate in a Research Study

Consent Form Version Date: 03/09/2021
IRB Study # 17-3348
Title of Study: Fructose-liver fat study
Principal Investigator: Saroja Voruganti
Principal Investigator Department: Nutrition Research Institute
Principal Investigator Phone number: 704-250-5009
Principal Investigator Email Address: saroja@email.unc.edu
Co-Investigators: Baba Mass, Brea Correll Nance

What are some general things you and your child should know about research studies?
You are being asked to allow your child to take part in a research study. To join the study is voluntary. You may refuse to give permission, or you may withdraw your permission for your child to be in the study, for any reason, without penalty. Even if you give your permission, your child can decide not to be in the study or to leave the study early.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the researcher, the health care provider, or the University of North Carolina-Chapel Hill. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study. You will be given a copy of this consent form. You and your child should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The purpose of this research study is to identify genetic factors that increase the risk of fat accumulation in the liver based on consumption of sugar drinks.

Are there any reasons your child should not be in this study?
Your child should not be in this study if he/she is not Caucasian, not between ages 12 and 19 years, has a history of alcohol abuse, drinks more than 7 sugar drinks per week, have diabetes or pre-diabetes, have adverse reaction to fructose or any sugar consumption, or have liver or kidney disease.

How many people will take part in this study?
There will be approximately 100 children in this research study.

How long will your child's part in this study last?
This study includes three phases: First phase is of 30-minute duration. Your child will be invited to take part in the second and third phase if he/she is selected based on your genetic makeup. The second and third phase will be of two days each, the first day being about 3 hours and the second day being 3.5 hours duration.

What will happen if your child takes part in the study?
Phase 1: Your child will be asked to provide informed consent, provide a saliva sample and fill out a short questionnaire including information related to her/his sugar intake. The saliva sample will be used to determine if he/she has a high or low genetic risk for fatty liver. If he/she does not have either a high or a low risk, he/she will not continue on to phase 2 of the study.

Phase 2: If your child is one of the 24 selected people,

Day 1: You and your child will visit University of North Carolina Nutrition Research Institute (UNC-NRI) from where study investigators will take you to the WakeForest Imaging center to scan your liver for fat accumulation. If your child's liver fat is more than normal, then he/she will not continue with the study. If your child is a female, then we will conduct a pregnancy test. If she is pregnant, the she will not continue with the study. Otherwise he/she will come back to NRI the next day for further steps.

Pregnancy testing is required for participation in this study; all girls age 12 and older or those older than 10 years who are menstruating, will be tested for pregnancy. Only those testing negative will be allowed to participate. If your child is 12 years and younger, we will share pregnancy test results with you. If your child is 13-17 years of age, we will share pregnancy test results with you if your child 1) agrees that we can share this information with you, 2) is pregnant and does not appear to understand the situation, becomes highly emotional or expresses the potential of harming herself or 3) your child discloses that they may be in potential harm from a partner or someone else due to the pregnancy

Day 2: Your child will first provide anthropometric (body weight, waist circumference, height and percent body fat), non-invasive ultrasound of the liver (fibroscan), and blood pressure measurements, 2) agree to have their blood and urine collected at 3 time-points (baseline, 1 hour and 3 hours later) and 4) complete questionnaires about their lifestyle, dietary patterns, and medical history.

Your child will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for the child for the evening prior to the participation. On the morning of day of day 2, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if your child does not want to be poked three times he/she can choose an in-dwelling catheter (flexible needle) to be placed in their arm for multiple blood draws. Blood sampling will be conducted by a trained phlebotomist. We will give your child about two 12 fluid ounces of sugar-sweetened beverage. Your child will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablepoons) of blood before your child drinks the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before your child drinks the beverage and then again at 1 hour and 3 hours later.

You/your child can decide to complete the questionnaires during the study visit, or can take them home and mail them back to the investigators. You/your child may also access our secure website with the username and password provided to you by the investigators and complete the questionnaires that way.

Week1-Week3: Your child will be given three weeks supply of sugar drinks. Each sugar drink is equal to 2 sodas and needs to be taken once daily. Your child should not drink any other sugary drinks during the three weeks.

Phase3: Provide anthropometric (body weight, waist circumference, height and percent body fat), fibroscan, and blood pressure measurements, and complete questionnaires about your lifestyle, dietary patterns, and medical history.

Visit 1: You and your child will visit NRI from where study investigators will take you both to the WakeForest Imaging center to scan your child's liver for fat accumulation.

Visit2: Your child will not be able to eat or drink 12 hours prior to the study visit. We will provide a meal for your child for the evening prior to your participation. On the morning of day of visit 1, we will collect blood through venipuncture which means blood will be drawn through a needle three times during the study. However, if your child does not want to be poked three times, he/she can choose an in-dwelling catheter (flexible needle) to be placed in their arm for multiple blood draws. Blood sampling will be conducted by a trained phlebotomist. We will give your child two 12 fluid ounces of sugar-sweetened beverage. Your child will need to drink it within 20 minutes. We will collect 24 ml. (approximately 1.5 tablepoons) of blood before he/she drinks the beverage and then again at 1 hour and 3 hours later for a total of 72 ml (approximately 5 tbsp). We will also collect urine samples before your child drinks the beverage and then again at 1 hour and 3 hours later.

What are the possible benefits from being in this study?
Research is designed to benefit society by gaining new knowledge. Your child will not benefit personally from being in this research study. However, the knowledge related to the genetic effects on prevalent metabolic diseases will help the community in finding new treatment options.

What are the possible risks or discomforts involved from being in this study?
The only invasive procedure in this study is blood drawing but there is no alternate way to obtain this information. To make the blood draws more comfortable, an in-dwelling catheter can be placed in your arm. If your child does not want a catheter, he/she will receive a needle stick for every blood draw but we will do our best to provide comfort during each blood draw. Blood draws can also cause dizziness and a feeling of nausea in some cases. Please let the investigators know whether you get sick during blood draws or if you react adversely to blood draws.

Because your child will be consuming drinks equal to 2 cans of soda every day for 3 weeks, there is a possibility of weight gain.

If it is known, through the clinical examination, that your child has a risk for certain metabolic disease we will contact you in confidence and advise you to consult your physician. There may be uncommon or previously unknown risks. You should report any problems to the researcher.

What if we learn about new findings or information during the study?
You and your child will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will information about your child be protected?
All data will be strictly confidential and will be stored with the Principal Investigator (Dr. Saroja Voruganti). All information will be coded and only the coded and anonymized data will be available to co-investigators for analysis. Participants will not be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

What if you or your child wants to stop before your child's part in the study is complete?
You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction, or has failed to follow instructions, or because the entire study has been stopped.

Will your child receive anything for being in this study?
This study has 3 phases. Your child will receive $25 for taking part in the first part of the study. Your child will receive $150 for taking part in the second phase and $150 for the third phase of the study. If your child participates but is unable to complete the acute challenge part of the study, he/she will receive $50 for your time and effort. If your child completes the acute challenge but not the 3-week intervention then he/she will receive $100 for their time and effort. If your child completes one week of the intervention, then he/she will receive $150 for their time and effort. However, no shows and cancellations will not receive any money.

Will it cost you anything for your child to be in this study?
It will not cost anything to be in this study.

What if you or your child has questions about this study?
You and your child have the right to ask, and have answered, any questions you may have about this research. If there are questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, contact the researchers listed on the first page of this form**.**

What if there are questions about your child's rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

Parent's Agreement:
I have read the information provided above. I have asked all the questions I have at this time. I voluntarily give permission to allow my child to participate in this research study.

_____
Printed name of research participant (child)

_____ _____
Signature of one parent Date

_____
Printed Name of the Parent

_____ _____
Signature of other parent Date

_____
Printed Name of the Parent

_____ _____
Signature of research team member obtaining permission Date

_____
Printed Name of the research team member obtaining permission