Title: A Feasibility Study of Tree Nut and Extra Virgin Olive Oil Supplementation to Improve Cardiometabolic Health
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Wake Forest®
School of Medicine

Department of Epidemiology and Prevention

A Feasibility Study of Tree Nut and Extra Virgin Olive Oil Supplementation to Improve Cardiometabolic Health

Informed Consent Form to Participate in Research

RESEARCH TEAM CONTACT INFORMATION:

For questions about research appointments, the research study, or other concerns, call the study team at:

Researcher Name: Lindsay Reynolds, PhD Phone Number: [redacted] Email Address: [redacted]	Study Coordinator: Sandra Norona Phone Number: [redacted] Email Address: [redacted]

SUMMARY

You are invited to participate in a research study. The purpose of this research is to find out if people aged 35 and older who meet the criteria for metabolic syndrome are interested in participating in a research study that requires them to eat tree nuts and extra virgin olive oil daily, and to find out what barriers or challenges and motivators participants encountered when trying to incorporate nuts and oils into their daily diets.

You are being invited to be in this study because you are an adult over 35 years of age with metabolic syndrome. Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. These conditions include high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Your participation in this research will involve 3 in-person visits and two phone call visits. Your participation will last about 4-5 weeks. You may be contacted by the study team and asked to discontinue study participation if the study reaches their goal of 50 completed study participants before your next scheduled study visit. If you are contacted and asked not to return, this will mean that your involvement in the study is complete and you do not need to return for additional study visits. Since there will be no other study related activities, no compensation will be provided for the final study visit.

Participation in this study will involve coming in to the Clinical Research Unit for the in-person study visits where you will have height, weight, blood pressure and waist circumference measurements, blood drawn, and we will collect information about your health behaviors and history. If you are eligible to take part in the study, you will come back for the Intervention visit, where you will have your blood drawn and you will be given a 4-week supply of tree nuts (unsalted walnuts, almonds and pistachios) and olive oil. The study staff member will give you information and guidance about how to incorporate the nuts and oil into your diet, and you will record whether or not you ate the study foods every day. All research studies involve some risks. A risk of this study that you should be aware of is minor side effects, mainly stomach upset,

bloating, nausea and weight gain. There is also a possibility that you may have an unknown allergy to the study foods and experience an allergic reaction. There is a possibility that you may benefit from participation in this study. Eating nuts and oils has been found to be help reverse metabolic syndrome, reduce waist size, and lower blood sugar levels.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. This is not a treatment study; your option is not to participate in the study. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Lindsay Reynolds, PhD. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study her contact information is: [redacted].
If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted]

INTRODUCTION

You are invited for an initial evaluation to be in a research study because you are an adult who is at least 35 years old with metabolic syndrome. Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. These conditions include high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Metabolic syndrome may also affect the genetic material in the cells in your body, a process known as epigenetic aging. Research studies are designed to gain scientific knowledge that may help other people in the future. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate in the initial evaluation and subsequent research study if eligible. Ask the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

Researchers in Spain have shown that people who ate a mixture of nuts and olive oil lowered their risk for having heart attacks and strokes and some were able to reverse metabolic syndrome. Before we can test if eating nuts and olive oil would have similar results in a large number of people living in the U.S., we have to find out if people are interested in participating in a study like this and if they are, whether they can eat the nuts and olive oil over a period of time. We are also interested in learning more about the relationship between epigenetic aging and eating nuts and olive oil. The purpose of this research study is to find out if people aged 35 and older who meet the criteria for metabolic syndrome are interested in participating in a research study that requires them to eat tree nuts and extra virgin olive oil daily, and to find out what barriers or challenges and motivators participants encountered when trying to incorporate nuts and oils into

their daily diets.

How Many People Will Take Part in the Study?

About 50 people from Forsyth County and the surrounding area will take part in this study.

What Is Involved in the Study?

If you qualify for this study and decide to participate, in addition to this in-person screening visit, you will be asked to participate in a four-week study involving daily olive oil and tree nut consumption. If eligible, you will be scheduled to come in to the clinic for two additional visits, one at the beginning of the nuts and oil study (intervention), and a second visit at the end of the four-week study (final visit). You will also receive two check-in phone call visits, approximately one week and two weeks after the baseline visit.

Baseline: In – Person Screening visit

You will come to the Clinical Research Unit for the in – person screening visit. During this visit, we will discuss the Informed Consent form and answer any questions you have about the study. If you agree to participate in the study we will have you sign the consent form and we will perform assessments to determine if you are eligible for the nuts and olive oil intervention. The following tests will be performed during the In-Person Screening visit:

- Measuring your height and weight
- Measuring your waist circumference
- Measuring your blood pressure, and
- Collecting a fasting blood sample. You will be asked not to eat or drink anything except water for 8 hours before the scheduled visit.
- You will also be asked to answer questions about your medical history, medication use and health behaviors. We will ask that you bring your medications with you to the initial visit.

Intervention visit

You will return to the Clinical Research Unit for your intervention visit. During your intervention visit:

- We will collect a fasting blood sample. You will be asked not to eat or drink anything except water for 8 hours before the scheduled visit.
- You will be given the full 4-week supply of tree nuts (unsalted walnuts, almonds and pistachios) and olive oil. The study staff member will give you information and guidance about how to eat approximately 1 ounce of nuts and 2 tablespoons of olive oil every day. The nuts will be in daily servings and we will ask you to measure 2 tablespoons of olive oil daily with a measuring spoon that will be provided.
- You will be asked to include the nuts and olive oil in your normal eating pattern and will be provided recipes and other information to help you replace other foods with the nuts and olive oil.

- You will be given a diary to track your intake of the study foods every day of the 4 week study.
- You will be asked to review the completed diary during your scheduled phone call visits which will take place approximately one week and two weeks after your intervention visit.

At the intervention visit, participants will also be randomized (like flipping a coin) to be placed into one of two study groups. In one group participants will receive nuts and olive oil plus they will learn about a concept called "epigenetic aging", that is, they will learn how genetic testing performed on blood samples can provide information on biological aging. The second group will receive the nuts and olive oil but will not learn more about epigenetic aging.

End of Week 1 and Week 2 Telephone Calls

You will receive a telephone call from a member of the study team after the first and second week. The purpose of the call will be to ask you questions about eating the nuts and olive oil and changes in your health

Final visit

The final study visit will take place at the Clinical Research Unit. As with the initial in-person screening visit, you will be asked not to eat or drink anything but water for eight hours before the final visit which will be scheduled in the morning.

During the final visit:

- We will measure your height, weight, waist circumference and blood pressure.
- We will collect a blood sample.
- You will also be asked to answer questions about your medical history and health behaviors.
- You will be asked to complete an Intervention Experience Assessment to get feedback about your experience in the study and challenges and motivating factors that influenced your ability to consume nuts and olive oil on a daily basis.
- You will be asked if we can contact you for future studies.
- If you were randomized to learn about epigenetic aging, you will be asked questions about your thoughts on the information provided to you.

HOW LONG WILL I BE IN THE STUDY?

Eligible participants will be in the nuts and oil intervention study for 4 weeks.

You may be contacted by the study team and asked to discontinue study participation if the study reaches their goal of 50 completed participants before you have attended your next scheduled study visit. If you are contacted and asked not to return, this will mean that your

involvement in the study is complete and you do not need to return for additional study visits. Since there will be no other study related activities, no compensation will be provided for the final study visit.

You can stop participating at any time without any health or safety consequences. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first.

STORAGE OF BIOLOGICAL SPECIMENS

IF YOU AGREE TO PARTICIPATE IN THIS STUDY, WE WILL COLLECT BLOOD SAMPLES. THESE SAMPLES WILL BE KEPT AND MAY BE USED IN FUTURE RESEARCH TO LEARN MORE ABOUT MARKERS OF HEALTH INFORMATION. THE SAMPLES WILL BE STORED AT THE WAKE FOREST SCHOOL OF MEDICINE IN WINSTON-SALEM, NC AND WILL BE GIVEN ONLY TO RESEARCHERS APPROVED BY LINDSAY REYNOLDS, PHD. AN INSTITUTIONAL REVIEW BOARD (IRB) MUST ALSO APPROVE ANY FUTURE RESEARCH STUDY USING YOUR SAMPLES. BIOLOGICAL SAMPLES WILL BE STORED WITH A UNIQUE IDENTIFIER AND WILL NOT INCLUDE ANY IDENTIFIABLE INFORMATION ABOUT YOU SUCH AS YOUR NAME, ADDRESS, TELEPHONE NUMBER, SOCIAL SECURITY NUMBER, MEDICAL RECORD NUMBER OR ANY OF THE IDENTIFIERS OUTLINED IN THE HIPAA PRIVACY RULE. THE UNIQUE IDENTIFIER WILL BE A RANDOMLY ASSIGNED NUMBER AND ONLY THE PRINCIPAL INVESTIGATOR WILL HAVE ACCESS TO THE CODE THAT LINKS THE UNIQUE IDENTIFIER TO YOU. YOUR NAME, ADDRESS, SOCIAL SECURITY NUMBER, ETC., WILL NEVER BE DISCLOSED TO FUTURE RESEARCHERS AND NEITHER WILL THE CODE THAT LINKS YOUR IDENTIFIERS TO THE SAMPLE. IN ORDER TO PARTICIPATE IN THIS STUDY, YOU MUST BE WILLING TO PROVIDE THESE SAMPLES FOR FUTURE RESEARCH.

The research that may be performed with your blood sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood will not affect your care.

Your blood sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

GENETIC TESTING

As part of this research study, you will be asked to provide biological specimens (blood). This study will examine genomic changes related to consuming nuts and olive oil. At some point in the future, we may be required to share genomic data with federal repositories. The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. These central banks store genetic information and give them to other qualified and approved researchers to do more studies. The data that we

share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at the Wake Forest Baptist Health. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository. We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future. The genetic data could be used to study a wide variety of diseases. In the future, research on your specimen may involve whole genome sequencing.

WHAT ARE THE RISKS OF THE STUDY?

The risk of harm or discomfort that may happen as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. You should discuss the risk of being in this study with the study staff.

Risks associated with the study intervention

Nuts and olive oil are generally recognized as safe and are consumed by adults in the general population on a regular basis. If you participate, the amount you will be given is similar to the range given to the participants in the study conducted in Spain, though they only consumed that amount of either nuts or olive oil. This amount was found to have only minor side effects, mainly stomach upset, bloating and nausea. None of the side effects were serious and these symptoms resolved. A Safety Monitor who is a physician will be reviewing the data from this research throughout the study.

Allergy - There is a slight risk that you may have an unknown allergy to nuts or olive oil and may therefore have an allergic reaction to one of these substances. Mild allergic symptoms that can occur include: raised red bumps of skin – hives, swelling of the lips, tingling of the throat and mouth, itchy skin and rash, runny nose, tightening of the throat, and digestive symptoms – cramps, stomach pain, nausea or vomiting. If you feel you are experiencing one of these mild allergic reactions, please contact the study team.

Consumption of tree nuts can also result in severe allergic reaction symptoms including: difficult or noisy breathing, swelling of the tongue, swelling or tightness of the throat, difficulty talking or a hoarse voice, wheeze or persistent cough, or persistent dizziness or collapse. If you feel you are experiencing one of these severe allergic reaction symptoms, please call 911 and seek immediate medical care. After treatment, please contact the study team.

Weight Gain - Because we are asking you to add the nuts and olive oil to your diet, there is also a risk that you could gain weight. If you decide to participate, you will be given information to help you replace foods that you normally eat with the nuts and olive oil to reduce the risk of you

gaining weight. If you feel you may be gaining weight, members of the study team will work with you to manage your food intake appropriately.

Risks associated with study procedures:

Blood Draw - You may experience discomfort, bruising and/or bleeding where the needle is inserted during a blood draw. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Blood pressure measurement - The squeezing of an inflated blood pressure cuff on your arm may be uncomfortable, but it should last only a few seconds

There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. We will do our best to protect your confidential information. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe. However, there is a slight risk of a breach of confidentiality.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is a possibility that you may benefit from participation in this study. Daily consumption of nuts and oils have been found to be help reverse metabolic syndrome, reduce waist circumference, and lower fasting glucose levels. We also hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?

This is not a treatment study. Your alternative is not to participate in this study.
You do not have to be in this study to receive this intervention. You should talk to your doctor about all the choices you have. Instead of being in this study, you can buy nuts and olive oil at the grocery store.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any information about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** height, weight, waist circumference, blood pressure, blood, and questionnaires about your health habits and medication.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), and the Department of Health and Human Services (DHHS).

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Monitors, auditors, IRB or other regulatory agencies will be granted direct access to your original medical record for verification of clinical trial procedures or data, without violating confidentiality and to the extent permitted by other applicable laws

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified.

You can tell Dr. Lindsay Reynolds that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Lindsay Reynolds, PhD
[redacted]

[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

Laboratory test results and other clinically relevant medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including the nuts and olive oil, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or

others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required.

CERTIFICATE OF CONFIDENTIALITY

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 child 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 Institutes of Health (NIH) 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.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $45 in the form of a ClincCard (re-loadable debit card) after completion of the following study visits: $20 for the first in-person study visit and $25 for the last in-person study visit. If you withdraw or are discontinued for any reason from the study before completion you will only be paid for the visits that you completed.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the Clinical and Translational Science Institute and Cardiovascular Sciences Center at Wake Forest School of Medicine. The study team has no financial interest in the outcome of this study.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy

the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Lindsay Reynolds at [redacted] or [redacted] (after hours).

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study. Clinically relevant research results will not be disclosed to you.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, call Dr. Lindsay Reynolds at [redacted] or [redacted] (after hours).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm