Assessing Gut Microbiota Mediated Health Outcomes of Whole Wheat and Its Major Bioactive Components

Informed Consent Form

NCT Number: NCT05318183

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The Ohio State University Consent to Participate in Research

Study Title: Assessing gut microbiota mediated health outcomes of whole wheat and its major bioactive components

Principal Investigator: Richard S. Bruno, Ph.D., R.D.

Sponsor: United States Department of Agriculture

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the

form. You are being asked to consider participating in this study for the reasons explained below.

Key Information About This Study

The following is a short summary to help you decide whether or not to be a part of this study. More detailed information is listed later in this form.

The purpose of this research is to understand why eating whole wheat bread lowers blood sugar in some people but not all people. We believe that this is due each person's unique profile of bacteria in gut. Differences in gut bacteria could metabolize whole wheat bread differently to improve blood sugar levels. If you choose to participate in this study, your involvement will span 8-12 weeks depending on your schedule. During this period, there will be 2 study phases. Each phase will be 2-weeks long. For each 2-week study phase, we will provide all your foods and beverages for you to eat. We will also be collecting blood from your arm at the beginning and at the end of each study phase. During each trial, we will also be asking you to collect your own fecal sample on two occasions at the beginning and end of each study phase and to also collect your own urine for 24-hours at the end of each study phase. We will provide all collection containers and gloves so that you can perform these tasks in a safe and sanitary manner. The primary risk of this study relates to the small initial pain, bruising, or lightheadedness you may experience when having your blood collected. There is also the inconvenience of having to collect your own fecal and urine samples. There are no costs to you to participate in this research. Benefits to you for participating include receiving all of your foods for approximately 1-month, blood levels of glucose, and information about your blood pressure and body weight.

1. Why is this study being done?

Prediabetes (high blood sugar) often occurs with other conditions — high blood pressure, excess body fat around the waist, and elevated blood cholesterol or triglyceride levels. Prediabetes can increase the risk of heart disease, stroke and diabetes. Research has shown positive benefits of whole grain foods to reduce some risks of disease. However, the health benefits can vary a lot between different people. Whole grains/whole wheat contains fiber and other health promoting compounds. Many studies support that whole grains/whole wheat improve human health directly from these compounds and/or from their metabolites that get generated by the bacteria in the human gut. Thus, the objective of this study is to investigate whether each person's gut bacteria influences the health benefits of whole wheat. This will help us to better understand the benefits of whole wheat in humans with prediabetes.

2. How many people will take part in this study?

Our goal is to recruit 40 men and women with prediabetes between 18-65 years of age. To meet this goal, we plan to screen up to 300 individuals.

3. What will happen if I take part in this study?

Screening

Before participating in this study, you will need to visit our study center located in Evans Hall on the Ohio State University campus for initial measures of your height, weight, waist circumference. We will also collect a small blood sample to make sure that you have fasting blood chemistries appropriate for this study. During this time, an experienced technician will measure your blood pressure and collect a small blood sample (10 mL, 0.66 tablespoon) from your arm. Within a week, we will provide you with your blood results. If your blood results and body weight measurements meet our study requirements, you will be invited to continue with the rest of the study procedures. If not, you will not be able to participate in our study.

Study Overview

This study consists of two study phases. Each phase is 2-weeks long and each phase will be separated by a 2-4 week period. In both study phases, we will be providing all your foods and beverages. Your meals will be mostly identical between each study phase except one phase will include two daily slices of whole wheat bread and the other phase will include to daily slices of white bread. The order in which you receive the diets containing whole wheat or white bread will be assigned by chance. The amount of food given to you will be customized based on your daily calorie needs. The meals will be cooked and ready to eat. Microwave instructions will be provided for any foods that need reheating. It is recommended (but not required) that you eat food provided to you so you can maintain the same weight throughout the study. It is important to our study that you consume the whole wheat bread/white bread provided. *If you are unable to consume all of the foods given, please prioritize eating the bread.* We will also give you a form to complete if you accidentally eat any foods/drinks that we did not provide to you.

If you participate in this study, we ask that you do not exercise for more than 5 hours per week throughout the entire study. In addition to eating a diet designed specifically for you, each study phase involves us collecting blood from you. During this entire study, including Phase 1 and Phase 2, and an initial health screening, we will be collecting a total amount of 318 mL of blood (about 1.34 cups). This amount of blood is safe for collection, but you should not donate blood during the course of this study or for 8 weeks after completing the study. Lastly, you will also collect your own urine and stool samples in a sanitary manner using collection kits that we will provide you. Activities that we will ask you to complete for each 2-week study phase are described below:

Study Phase 1.

- *Visit 1 / Day 1:* During this visit, we will measure your height, weight, and blood pressure. We will also collect a fasting blood sample (10 mL blood or 0.66 tablespoon). During this visit, you will also pick-up daily meals that you will eat for the next 3-4 days. Lastly, you will provide us a stool sample collected with the past 24-hours using a stool collection kit that we will provide you. The kit has a plastic

container that can be placed underneath the toilet seat to collect your stool sample. Gloves and a waste bag are also provided to prevent any possible contamination.

- *Visit 2 / Day 3:* You will visit the study center briefly to pick-up meals that you will eat for the next 3-4 days. You will also return all uneaten foods and containers to the study team so that we can determine actual food consumption during the past few days.

- *Visit 3 / Day 7:* You will visit the study center briefly to pick-up meals that you will eat for the next few days. You will also return all uneaten foods and containers to the study team so that we can determine actual food consumption during the past few days. During this visit, we will also take your body weight again and ask you to collect your own urine sample in a container provided to you.

- *Visit 4 / Day 10:* You will visit the study center briefly to pick-up meals that you will eat for the next few days. You will also return all uneaten foods and containers to the study team so that we can determine actual food consumption during the past few days. We will also provide you a stool collection kit that you will need to use before your next visit to our study center.

- *Visit 5 / Day 14:* You will visit the study center in the fasting state for approximately 4hours. You will provide us a fecal sample that was self-collected during the past 24hours. You will also return all uneaten foods and containers to the study team so that we can determine actual food consumption during the past few days. Next, we will ask you to collect your own urine sample in a container provided to you. We will then measure your height, weight, and blood pressure and collect a blood sample. We will then ask you to simultaneously complete an oral glucose tolerance test and test that assesses how leaky your gut is. These tests involve you drinking a solution containing glucose and artificial sweeteners. This drink will be sweet similar to a sugary drink (e.g. Kool-Aid). We will then collect a blood sample from a catheter in your arm every 30minutes for 3-hours. After each blood sample is collected, the catheter will be flushed with sterile saline to prevent clots and to minimize the likelihood of having to insert a needle again. During each blood collection, we will be collecting about 15 mL blood (1 tablespoon) or about 140 mL (0.6 cups) of total blood on this day. Once completed, we will then provide you foods and beverages to eat for the next 24-hours. For 24-hours after you drink the sugar solution, we will also provide you urine collection containers to collect all of your urine. During this time, we ask that you consume only the foods we provide because they will not contain any artificial sweeteners.

- *Visit 6 / Day 15:* You will return to the study center to provide the urine that you collected for the past 24-hours. This completes Phase 1 of the study.

Wash-out Period.

- Phase 1 and Phase 2 will be separated by at least two-weeks for men. However, this period may be extended for women to enable testing during the same phase of the menstrual cycle. During this wash-out period, you can resume your normal diet and activities.

Study Phase 2.

- After the wash-out period, you will be asked to return to our study center to complete Phase 2 of the study. All activities and procedures for Phase 2 will be identical to those of Phase 1 except that you diet will change. If you received whole wheat bread in Phase 1, you would now receive white bread for Phase 2. If you received white bread in Phase 1, you would now receive whole wheat bread.

Study Completion

- On Day 15 (Visit 6) of Phase 2, your involvement in the study is completed. We will provide you a check to compensate you for participating in the study. Details of compensation are described in Section 12 of this form.

- If you are interested in learning about the final results of the study, we will provide you a form to record your email address. When available, a copy of the published study results will be emailed to you.

Blood, Urine, and Stool Sample Storage Agreement

All blood samples collected for this study will be analyzed for glucose, insulin, total and HDL-C, triglyceride, endotoxin, and proteins and/or genes associated with inflammation (TLR4, CD14, MD2, MyD88, p65, IL-1, IL-6, IL-8, TNFα, MCP-1) and various human metabolites. Urine samples will be analyzed for artificial sweeteners and compounds found in bread. Stool samples will be analyzed for short chain fatty acids, inflammatory markers (calprotectin, myeloperoxidase), fecal metabolites and microbiota (naturally abundant bacteria in the gut) composition. Any remaining samples will be stored up to 5 years at our study center. We kindly request that you allow us to store your samples for future analysis specifically related to this study. Storage of samples is optional and you may complete the study without agreeing to the storage of samples.

Do you agree to allow us to store any remaining blood, urine, and stool samples for additional future measurements? Please circle your response and provide your initials below:

YES NO _____(Participant's Initials) _____Date

4. How long will I be in the study?

You are required to visit the study center at least 6 times per study phase, for a total of 12 times. Prior to joining the study, you will complete a screening visit, which will take about 1

hour. Most visits to the study center will require about 10-30 minutes. On the day that you complete the glucose tolerance and leaky gut tests, we expect you to be at the study center for about 4 hours. All study procedures will be completed identically in each study phase (whole wheat bread and white bread). Overall, we anticipate that you will commit about 13 hours over the course of about 6-12 weeks to complete the study, depending on your availability.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University.

6. What risks, side effects or discomforts can I expect from being in the study? The primary inconvenience for you is that you must visit our study center 14 times over the course of the entire study. You will need to limit your exercise to less than 5 hours per week throughout the study. Additionally, you may consume only the food and beverage products provided to you throughout each two-week intervention period.

Blood Collection. During the blood drawing aspect of this investigation, only experienced technicians will be responsible for inserting all catheters and needles as well as collecting blood samples. All blood drawing materials will be sterile and sanitary techniques will be used. You may experience a small initial pain from insertion of the needle and bruising may occasionally occur after the procedures are completed. In addition, you may experience lightheadedness or feel faint which is common when people donate blood. At study visit 5, we will be collecting about 140 mL or 0.6 cups of blood. We do not foresee any additional significant risks with collecting this amount of blood, other than the possible risks stated previously. During study visit 5, you will need to keep the flexible catheter inserted for 3 hours, which may lead to some discomfort.

Sugar Test Beverage. The sugar test beverage contains a mixture of non-digestible sugars that are safe for human consumption. Although we expect no adverse effects, you may experience slight gastrointestinal discomfort after consuming the beverage.

Urine and Stool Sample Collection. During study visit 5, we will ask you to collect your urine for 24 hours. We will also ask you to provide a stool sample taken at the beginning of the intervention and on day 13. We will provide you with urine collection containers and show you how to use the stool collection kits to collect a stool sample safely and hygienically. If you do not feel comfortable collecting your own urine or stool, we ask that you do not participate in this study.

Confidentiality. To maintain your confidentiality, a number (i.e. code) will be assigned to you. This “code” will only be available to research personnel and any records containing your name will be stored in a locked filing cabinet within a lockable office or on a password

protected computer in the principal investigator's laboratory or office. Research personnel under the supervision of the principal investigator and the principal investigator will be the only individuals that have access to this information.

Whole Genome Sequencing. This research does not involve whole genome sequencing of your DNA. Genetic analysis in the present is limited to your gut microbiota to determine the bacteria present in your gastrointestinal tract. This information cannot be used to identify you. Ask the study team if you have questions.

7. What benefits can I expect from being in the study?

Although consumption of whole wheat bread is expected to have a positive effect, there is no guarantee the results will directly benefit you. You will be provided with your screening blood testing results as categorical information, because the results are for research purposes and cannot be used to provide a clinical diagnosis of disease. In addition, we will provide information regarding your blood pressure, height, weight, and body mass index. If you are interested in learning more about your results during the study, we would be happy to email you a copy of the final study findings that are compiled in an anonymous manner once we have published our findings. Overall, this study is expected to advance our understanding how whole wheat bread favorably affects blood glucose and inflammation and the potential role of gut bacteria to influence these health benefits. This information is of great importance to increase an understanding of the potential health benefits of whole wheat bread for improving metabolic health.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information; •
  The sponsor supporting the study, their agents or study monitors; and •
  Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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 the website at any time.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. Will my de-identified information and bio-specimens be used or shared for future research?

Yes, they may be used or shared with other researchers without your additional informed consent.

11. What are the costs of taking part in this study?

There will be no costs for participating in this study except those needed for transportation to and from the OSU campus.

12. Will I be paid for taking part in this study?

If you complete the study in its entirety and provide all requested blood, stool, and urine samples and food records, and complete the two 2-week interventions and associated tests, you may receive up to $350 (as a check) at the completion of the study. The check will be given at your final study visit. Parking for each visit following acceptance into the study will be paid for by a parking pass. For each of the test periods following the informed consent and screening meeting, you will be paid in the following manner:

Phase 1 (up to $60):

- *Visit 1 (Day 1):* $10 will be provided for visiting our study center, providing a fasted blood sample, and having measurements of height, weight, and blood pressure taken
- *Visit 3 (Day 7):* $10 will be provided for visiting our study center, having measurements of height, weight, and blood pressure taken
- *Visit 5 (Day 14):* $30 will be provided for a 3-hour oral glucose tolerance testing session including providing blood samples and a stool sample.

- *Visit 6 (Day 15):* $10 will be provided for dropping off 24-hour urine sample collection

Phase 2 (up to $190):

- *Visit 1 (Day 1):* $30 will be provided for visiting our study center, providing a fasted blood sample, and having measurements of height, weight, and blood pressure taken
- *Visit 3 (Day 7):* $30 will be provided for visiting our study center, and having measurements of height, weight, and blood pressure taken
- *Visit 5 (Day 14):* $100 will be provided for a 3-hour metabolic testing session including providing blood samples and a stool sample
- *Visit 6 (Day 15):* $30 will be provided for dropping off 24-hour urine sample collection

Study Bonus:

If you complete the entire study and provide all of the requested materials, you will be provided a $100 bonus, which will bring your total compensation to $350. This will be given to you in the form of a check. If you withdraw or are dismissed from our study, you will be compensated for the completed aspects as indicated above.

Please note that by law, all payments are considered taxable income.

13. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

14. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of research participants.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact Dr. Richard Bruno (Principal Investigator; 614-292-5522; bruno.27@osu.edu).

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a studyrelated injury, you may contact Dr. Richard Bruno (Principal Investigator; 614-292-5522; bruno.27@osu.edu).

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form**.**

Printed name of participant	**Signature of participant**
	AM/PM
	Date and time
Printed name of person authorized to consent for participant (when applicable)	**Signature of person authorized to consent for participant (when applicable)**
	AM/PM
Relationship to the participant	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time