Cardiometabolic Effects of Pecans as a Snack
NCT05071807
September 19,2023

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Cardiometabolic effects of including pecans as a snack to improve diet quality: a randomized controlled study

Principal Investigator:
Name: Kristina Petersen
Department: Nutritional Sciences
Telephone: 814-865-7206
E-mail Address: kup63@psu.edu

Version Date:

Provide a version date for this document. This date must be updated each time this document is submitted to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

September 19,2023

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual", under "ClinicalTrials.gov" for more information.

NCT05071807

Important Instructions for Using This Protocol Template:

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. **GENERAL INSTRUCTIONS:**
   - Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
   - Do not change the protocol template version date located in the footer of this document.
   - Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
   - **GRAY INSTRUCTIONAL BOXES:** Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
     - **Do NOT delete the instructional boxes from the final version of the protocol.**
   - Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.

2. **CATS IRB LIBRARY:**
   - Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (http://irb.psu.edu).

3. **PROTOCOL REVISIONS:**
   - When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the guides available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.
   - Update the Version Date on page 1 each time this document is submitted to the IRB office with revisions.

If you need help…

All locations:
Human Research Protection Program
Office for Research Protections

The 330 Building, Suite 205
University Park, PA 16802-7014
Phone: 814-865-1775
Fax: 814-863-8699
Email: irb-orp@psu.edu
https://www.research.psu.edu/irb

Table of Contents

1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

The purpose of the proposed study is to examine how replacement of habitually consumed snack foods in the U.S. with 2 oz./day of pecans affects markers of peripheral vascular health, lipids and lipoproteins, blood pressure, and glycemic control compared to usual U.S. intake.

The aims of the study are as follows:
1) To evaluate whether consuming 2 oz/day of pecans as a snack improves flow mediated dilation compared with habitual intake in individuals at elevated risk for cardiovascular disease;
2 To assess changes in pulse wave velocity, lipids and lipoproteins (concentration, particle size and number), blood pressure (central and peripheral) and glycemic control in each group.

Hypothesis:
It is hypothesized that replacement of typical snack foods with 2 oz./day of pecans will improve peripheral vascular assessments, lipid and lipoprotein profile and glycemic control compared to habitual average American intake.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

Flow Mediated Dilation (FMD)

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Lipids and Lipoproteins (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides)
Lipoprotein particle size and number (LDL-cholesterol, HDL-cholesterol, VLDL and chylomicrons)
Pulse Wave Velocity (PWV)
Peripheral and Central Blood Pressure
Insulin, HbA1c and Fasting Glucose
Dietary intake of macronutrients, nutrients, and food groups
Diet Quality
Gut Microbiota composition

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard

of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the study procedure is available to patient without taking part in the study.

Current Dietary Guidelines for general health and prevention of chronic disease recommend a healthy dietary pattern U.S. Department of Health and Human Services (2016). In the U.S., habitual dietary patterns do not align with recommended health dietary patterns. Further, diet quality is suboptimal and thus strategies are needed to improve overall diet quality. The proposed trial aims to examine the cardiometabolic effects of pecans, when replacing a habitual snack. This trial will test the hypothesis that dietary incorporation of pecans to replace typical U.S. snack foods will improve diet quality and confer cardiometabolic benefits.

Pecans have the highest polyphenol content of any nut containing 1816 mg/100g (Ros, 2015). A significant proportion of the polyphenol content is flavanols (494 mg/100g), which are present in higher quantities than dark chocolate (246 mg/100g), blueberries (332 mg/100g) and red wine (313 mg/100g) (Gu et al., 2004). A meta-analysis of 11 studies showed that flow mediated dilation (FMD), a measure of endothelial function, increased by 1.34% after 2-18 weeks of consuming chocolate/cocoa/flavanols (Hooper et al., 2012). This change in FMD is clinically significant; for every 1% increase in FMD, the risk of CVD is reduced by 12% (Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015). Furthermore, Balzer et al. showed flavanol rich cocoa containing 371 mg or 963 mg of flavanols improved FMD for 2 to 3 hours after consumption; consumption of 963 mg of cocoa flavonols for 30 days increased FMD by ~30% (Balzer et al., 2008). In the proposed study, the subjects will consume approximately 212 mg of flavanols (781 mg total polyphenols) from pecans as part of the healthy dietary pattern. Therefore, based on previous studies of phenolic rich foods, we hypothesize that the polyphenols in pecans will act on the vasculature to improve endothelial function.

Nuts, including walnuts, almonds, hazelnuts, pistachios and peanuts, improve endothelial function (Casas-Agustench, Lopez-Uriarte, Ros, Bullo, & Salas-Salvado, 2011; Neale, Tapsell, Guan, & Batterham, 2017), lipids and lipoproteins (Del Gobbo, Falk, Feldman, Lewis, & Mozaffarian, 2015), and glycemic control (Tindall, Johnston, Kris-Etherton, & Petersen, 2019; Viguiliouk et al., 2014). Previous studies have not investigated the effect of pecans on endothelial function. Three studies have shown that pecans tended to reduce total and LDL-cholesterol when consumed for 4 or 8 weeks, compared to a control diet without nuts (McKay, Eliasziw, Chen, & Blumberg, 2018; Morgan & Clayshulte, 2000; Rajaram, Burke, Connell, Myint, & Sabaté, 2001), which would be expected to improve vascular health. Furthermore, Hudthagosol et al. showed that 90 g of whole pecans or 90 g of blended pecans increased postprandial plasma levels of phenolic acid and flavanols, increased antioxidant capacity and decreased LDL-cholesterol oxidation, compared to an isocaloric macronutrient matched meal (Hudthagosol et al., 2011). In this study, vascular health was not measured. However, based on the increase in total plasma phenolic acid and flavanols is it likely that endothelial function would have been greater (improved) after consumption of the pecan-containing meals compared with the control meal.

Previous work from our lab has shown that foods rich in phenolic compounds exert health effects beyond those expected based on the macronutrient profile. For example, in a randomized, crossover controlled feeding study, a moderate fat diet (34% fat, 6% SFA, 17% MUFA, 9% PUFA, 49% CHO, 16% PRO) containing one-avocado per day lowered atherogenic lipids and lipoproteins more than a matched moderate fat diet without avocado (Wang, Bordi, Fleming, Hill, & Kris-Etherton, 2015). Specifically, the moderate fat diet containing one-avocado per day lowered LDL-cholesterol and non-HDL cholesterol (−13.5 mg/dL, −14.6 mg/dL), relative to baseline and to a greater extent (P<0.05) than the matched moderate fat diet devoid of avocado (−8.3 mg/dL, −8.7 mg/dL) and a low fat (LF; −7.4 mg/dL, −4.8 mg/dL) control diet. The greater improvements in lipids and lipoproteins with the moderate-fat diet containing avocado vs. the matched moderate-fat diet without avocado suggests beneficial effects beyond the fatty acid profile of the avocado; it is hypothesized that the bioactive compounds and the fiber content of avocados may explain the results of this previous study.

Similarly, in a randomized, crossover controlled feeding study comparing a heart healthy diet with walnuts to a fatty acid matched diet devoid of walnuts, and a diet lower in alpha-linoleic acid (ALA) and proportionately higher in oleic acid, we observed greater total cholesterol and LDL-cholesterol lowering *(unpublished)* and a greater reduction in aortic diastolic blood pressure (A. M. Tindall et al., 2019) with the walnut containing heart healthy diet vs. the low ALA diet; no difference was detected between the walnut containing diet and the fatty acid matched diet devoid of walnuts, and the fatty acid matched diet devoid of walnuts and the low ALA diet. This suggests that the fatty acid component of walnuts may not explain the full effect that we observed.

Based on these studies, we hypothesize that greater improvements in risk factors for cardiometabolic disease will be observed with incorporation of pecan into and average American diets vs. the typical U.S. diet. This research aligns with the current focus on food-based recommendations, by authoritative organizations, because of the inherent limitations associated with nutrient-focused recommendations. Furthermore, evidence generated may be used to support food-based recommendations for pecans, and since 2 oz/day (14 oz-eq/week) of pecans will be provided, the findings may be used to support higher intake recommendations for nuts, specifically pecans. The 2020-2025 Dietary Guidelines for Americans recommends (5 oz.-eq/week of nuts, seeds and soy at 2000 kcal).

2.2 Previous Data

Describe any relevant preliminary data.

Previous work from our lab has shown that foods rich in phenolic compounds exert health effects beyond those expected based on the macronutrient profile (Wang et al., 2015). In another randomized, crossover controlled feeding study comparing a heart healthy diet with walnuts to a fatty acid matched diet devoid of walnuts, and a diet lower in alpha-linoleic acid (ALA) and proportionately higher in oleic acid, we observed greater total cholesterol and LDL-cholesterol lowering and a greater reduction in aortic diastolic blood pressure (A. M. Tindall et al., 2019) with the walnut containing heart healthy diet vs. the low ALA diet; no difference was detected between the walnut containing diet and the fatty acid matched diet devoid of walnuts, and the fatty acid matched diet devoid of walnuts and the low ALA diet. This suggests that the fatty acid component of walnuts may not explain the full effect that we observed.
A significant proportion of the polyphenol content is flavanols (494 mg/100g), which are present in pecans in higher quantities than dark chocolate (246 mg/100g), blueberries (332 mg/100g) and red wine (313 mg/100g) (Gu et al., 2004). A meta-analysis of 11 studies showed that flow mediated dilation (FMD), a measure of endothelial function, increased by 1.34% after 2-18 weeks of consuming chocolate/cocoa/flavanols (Hooper et al., 2012).
Based on these studies, we hypothesize that greater improvements in risk factors for cardiometabolic disease will be detected following consumption of the average American diet with pecans versus typical US dietary intake.

2.3 Study Rationale

Provide the scientific rationale for the research.

A study with this design would provide the first empirical evidence to directly support the inclusion of pecans in a recommended healthy dietary pattern. In addition to providing evidence about the cardiometabolic effects of using pecans to improve the diet quality of an average American diet, this study will provide a feasible food-based approach that may be used to lower CVD risk.

Approximately, 50% of Americans are at risk for CVD (29) and therefore, the findings from this study will be of direct relevance to many Americans. Specifically, the results will be of interest to individuals who are managing their elevated CVD risk with lifestyle strategies and pharmacotherapy; this study will test another lifestyle strategy that can be implemented to lower CVD risk.

The findings of this trial utilizing a non-pharmaceutical approach will be applicable to overweight and obese adults living with one or more symptoms of metabolic syndrome and are therefore at increased risk of cardiovascular disease in the US, and thus will be of substantial public interest.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

[Do not type here]

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

1) 25-70 years of age
2) BMI 25-40 kg/m^2
3) ≥ 1 criterion for metabolic syndrome (i.e., waist circumference ≥ 94 cm men or ≥ 80 cm women; triglycerides ≥150 mg/dL; HDL-cholesterol ≤ 40 mg/dL men or ≤ 50 mg/dL women; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; fasting plasma glucose ≥100 mg/dL) at screening.

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

1) Current use of tobacco-containing products or (≤6 months) cessation
2) Allergy/sensitivity/intolerance/dislike of study foods
3) Women who are pregnant, lactating, planning to become pregnant or have given birth in the past year

4) Individuals who have had a cardiovascular event (heart attack, revascularization, stroke), or have a history of heart failure, liver, kidney, autoimmune diseases or inflammatory conditions such as gastrointestinal disorders or rheumatoid arthritis.
5) Type 1 or type 2 diabetes
6) Unstable weight ≥10% body weight for 6 months prior to enrollment
7) Systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg at screening
8) Fasting blood glucose ≥126 mg/dL at screening
9) Triglycerides ≥350 mg/dL at screening
10) Taking any medications known to affect lipids, blood pressure, or blood glucose levels
11) Diagnosed inflammatory conditions or taking prescribed anti-inflammatory medications
12) Use of antibiotics within the prior 8 weeks
13) Taking supplements (e.g., psyllium, fish oil, soy lecithin, and phytoestrogens) and botanicals known to affect study outcomes and not willing to cease for the duration of the study
14) Individuals consuming >14 alcoholic drinks/week, and not willing to avoid alcohol consumption for 48 hours prior to test visit
15) Pre-menopausal women who do not have a regular menstrual cycle of 25-35 days
16) PI discretion

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Failure to comply with study procedures.
Participant withdraws consent.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

No safety concerns; no reason for follow-up. If consent is withdrawn no data from the participant will be used. Otherwise, if consent is not withdrawn, data from individuals who withdraw from the study may be used in an intent-to-treat analysis but another individual will be enrolled for each participant who drops out to ensure that an adequate sample size (with complete data) is reached.

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

[Do not type here]

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Flyer/posters will be placed in campus buildings and facilities as well as the surrounding area (gyms, churches, supermarkets, coffee shops, offices of health care providers etc.) to identify potential subjects residing in and around the State College. Ads will also be placed in the local papers, magazines (e.g., Centre Daily Times) and coupon mailers (e.g. Valpak), which are distributed to residential homes. In addition, radio ads will be run. Websites (e.g. http://clinicaltrials.gov/, Facebook, Craig's List, StudyFinder), and PSU listservs will be used to advertise the study. We will register for and utilize PALS database to contact participants as well. We also will contact individuals who have participated in previous studies and indicated to our research group that they are interested in participating in future studies. A letter to local businesses or organization may be utilized requesting they share study details with their members/employees if permitted.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

[Do not type here]

4.2.1 How potential subjects will be recruited.

Public advertisements (flyers/posters/ newspaper ads/circulars/ websites and social media/ radio/listservs) in the local community (State College/ University Park area)
A letter to local businesses or organizations requesting they share study details with their members/employees e.g. gyms, health clubs, social organizations, businesses located downtown or in the surrounding area.
StudyFinder
Telephone or email will be used to contact individuals who have participated in previous studies and indicated to our research group that they are interested in participating in future studies
People who are in the PALS database will be contacted using the verbiage in document PALS_Statement.doc(0.01)

4.2.2 Where potential subjects will be recruited.

University Park and State College PA and surrounding areas.

4.2.3 When potential subjects will be recruited.

As soon as the protocol is IRB approved, recruitment will commence and continue until the target sample size is enrolled.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Verbal screening consent will be obtained prior to the telephone screening being conducted. During the telephone screening a brief description of the study will be provided and the subject will provide vfloerbal consent to answer screening questions. If the individual agrees, some preliminary screening questions will be asked to establish whether the person is likely eligible for the study. If they are, a screening appointment will be scheduled at the Clinical Research Center (CRC). At this appointment, before any procedures take place, written informed consent will be obtained.

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** ***[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **Exempt Research at all Locations Except Penn State Health and the College of Medicine: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312- Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):**

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the records that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Verbal consent will be obtained prior to the telephone screening in a private room at Chandlee Laboratory or in a private room at the Clinical Research Center, Noll Laboratory.

Informed consent will be obtained at the Clinical Research Center, Noll Laboratory in a private room at the screening appointment prior to any screening procedures taking place.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Study staff, coordinators, and investigators who are fully trained in the recruiting process will respond to potential participants during recruitment so as to avoid any coercion or undue influence.

Participation is voluntary and participants can withdraw at any time. Participants will be emailed a copy of the written consent form, at the time their screening appointment is scheduled, and be asked to read it prior to their visit. At the screening visit, a study coordinator will ask the participant if they had a chance to read the consent form prior to the visit. If not, they will be given time to read the written consent form. A study coordinator will then go through the written consent form with the participant, allowing time for the participant to ask questions throughout.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Not applicable

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

Verbal Script see uploaded Verbal Consent 6-18-21.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

Not applicable

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

Not applicable

5.4.3 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Not applicable

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

Not applicable

5.5.2 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

Prospective subjects who do not understand English will not be enrolled.

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[Do not type here]

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☒ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☐ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a

waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Not applicable

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Not applicable

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Not applicable

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Not applicable.

7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

[Do not type here]

7.1 Study Design

Describe and explain the study design.

A two-arm randomized parallel study is proposed. Subjects will be randomized to one of the following attention and resource matched conditions for approximately 12-weeks: 1) education to consume 2 oz./day of pecans in place of the snacks they usually eat (AAD+P); 2) continue consuming their current diet (AAD) with provision gift cards worth $30 monthly (equivalent value to the pecans) and matched contact with study personnel.

Assessment of outcomes will occur at baseline and the end of the treatment period (week 12). Pre-menopausal women will be scheduled for testing within 7 days of starting their menstrual period to control for hormonal effects on vascular function. Therefore, the treatment periods may be adjusted as needed. At the baseline and 12-weeks two blood samples will be collected (separated by at least 24-hours) for endpoint analysis. Weight will be measured on both days at each timepoint. Flow mediated dilation, central and peripheral blood pressure and pulse wave velocity will be measured on one day at each time point. Diet intake will be assessed at baseline, week 6, and week 12 using 24-hour recalls. Subjects will also provide a fecal collection at baseline and 12 weeks.

7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

[Type protocol text here]

7.2.1 Visit 1 or Day 1 or Pre-test, etc.

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

Participants will be consented prior to any screening activities.
Screening: This visit will occur at the Clinical Research Center, Noll Laboratory. The clinical visit will consist of filling out forms (medical history, personal information); measuring waist circumference and height and weight so that BMI can be calculated and blood pressure will be measured to determine eligibility. Women of child-bearing potential will provide a urine sample for a pregnancy test. A blood sample will be taken and a complete blood count, and a blood lipid panel will be performed (approximately 19 ml of blood or ~1.25 tablespoon will be taken). If the initial blood draw is unsuccessful it may need to be repeated, with permission from the participant. In addition, if a potential participant takes thyroid medicine they must provide a current (within 6 months) lab test. If they do not have one, an extra 3.5 ml (0.2 Tbsp) of blood will be taken to conduct a thyroid test. If all eligibility criteria are met, participants will be scheduled for their baseline measurements. Baseline visits typically occur within 1-2 weeks following the screening appointment. Participants will be provided with one of two standardized meals with foods commonly consumed in the American diet prepared in the metabolic diet center kitchen to consume the evening before their Day 2 visit. The meal options will be Mediterranean chicken with potatoes and broccoli OR a black bean quesadilla with broccoli.

7.2.2 Visit 2 or Day 2 or Post-test, etc. (If applicable)

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

*Vascular testing may occur on day 1 or day 2 based on participant's availability

Baseline and Endpoint Measurements (Day 1)
Measures will be collected at baseline and 12 weeks. At each timepoint, fasting blood samples will be collected for analysis of biochemical endpoints. Body weight will be taken, and vascular health assessments will be performed at baseline and week 12. Participants will also complete a fecal collection at the beginning and end of the treatment period. Participants will complete three, 24-hour dietary recalls at baseline, week 6 and week 12 for a total of 9 dietary recalls. Participants will be provided a standardized meal for dinner.

Central and peripheral blood pressure: Following a 5-minute rest period, brachial artery systolic and diastolic blood pressure will be measured in the left arm using an automated blood pressure cuff. The cuff will reinflate and obtain a pulse wave form. Central blood pressure and wave reflection characteristics (augmentation index) will then be derived from the pressure waveforms using a validated transfer function with a SphygmoCor System (AtCor Medical, Sydney, Australia). This test will be performed in triplicate.

Pulse Wave Velocity: Arterial stiffness will be assessed by calculating the pulse wave velocity (PWV) between the carotid and femoral arteries while in the supine position. A cuff will be placed on the participant's thigh. The cuff will inflate during the test to record the pulse waveform in the femoral artery. A simultaneous measurement of the carotid artery pressure waveform will be obtained by an applanation tonometry sensor manually held in place above the carotid artery. PWV will subsequently be calculated by dividing the linear distance between the carotid and femoral sites by the transit time using the SphygmoCor system (AtCor Medical, Sydney Australia). This measurement will be performed in triplicate.

Plasma/serum analysis: In addition to the blood taken at screening, 12 hour fasting blood samples also will be taken. Approximately 45 ml (about 3 Tbsp) will be collected at each visit. A typical American Red Cross blood donation is 1 pint (500 ml). Blood may be analyzed for the following: blood lipids and lipoprotein concentration, particle number and size, glucose and insulin, other markers of glycemia, cholesterol metabolism, and/or inflammation.

Fecal collection: At baseline and the end of each treatment period, participants will be asked to collect a stool sample (~50 g). They will be provided with a stool sample kit and detailed instructions for collection of a clean sample on Day 1 of testing and asked to bring in the collected sample on Day 2; if an individual is not able collect the sample within this timeframe alternative arrangements will be made to accommodate the subject. Fecal samples will be analyzed for gut bacteria composition (gut microbiome).

7.2.3 Day 2 of Baseline and Endpoint Measures

On day 2 of baseline and endpoint visits, which occur approximately 24 hours after day 1 testing, a fasting blood sample will be collected and flow mediated dilation measures will be taken. Body weight will be taken. Fecal sample collection will be brought to the visit by the subject.

Flow mediated dilation**:** Study subjects will undergo endothelial health assessment by FMD at baseline (beginning of study) and end of each intervention period. The technique of FMD is a non-invasive test that assesses endothelium-dependent dilatation in response to increased blood flow. Blood flow is induced by inflation and deflation of a cuff on the forearm. The cuff should be inflated to suprasystolic pressures in order to occlude the brachial artery. A pressure of 250 mmHg is a standard pressure used by many research groups. B-mode ultrasound is used to assess endothelium-dependent vasodilation.

Plasma/serum analysis: A 12 hour fasting blood sample will be taken. Approximately 45 ml (about 3 Tbsp) will be collected at each visit. A typical American Red Cross blood donation is 1 pint (500 ml). Blood may be analyzed for the following: blood lipids and lipoprotein concentration, particle number and size, glucose and insulin, other markers of glycemia, cholesterol metabolism, and/or inflammation.

7.2.4 Monthly study food or gift card

Monthly, participants will coordinate pick up times for study food or gift card with study personnel at Penn State Metabolic Diet Study Center. Depending on Group, the script on "Usual Care Group Instructions-Marcella-6-18-21" or "Pecan Group Instructions-Marcella-6-18-21" will be used. Participants will also return compliance tracking sheets at months 2 and 3 (see attached "Daily monitoring form pecan condition-6-18-2021" or "Daily monitoring for usual care condition-6-18-2021) to identify if/when and how the pecans are being consumed.

Daily monitoring form: Participants will complete daily monitoring forms regarding consumption of pecans (test food)/ food consumed during the usual care condition, changes in medication or health during the study. When they pick up their test food monthly, they will be provided with the daily monitoring forms and asked to return the completed forms the next time they pick up food. Participants will also receive a phone call biweekly to ensure compliance.

7.2.5 24-hour dietary recalls

Dietary intake: Three, 24-hour recalls will be administered in the week prior to baseline, week 6, and week 12 of the study using the Automated Self-Administered 24-Hour (ASA24®) Dietary Assessment Tool. This is an online system where participants will provide information about all foods, beverages and supplements consumed during the previous day. This system generates food group and nutrient data from the 24- hour recalls. These data will be used for calculation of diet quality assessed by the Healthy Eating Index 2015 (4).

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Each participant will be involved in the study for approximately 12 weeks. Pre-menopausal women will be scheduled for testing within 7 days of starting their menstrual period to control for hormonal effects on vascular function; the treatment period will be adjusted accordingly in pre-menopausal women. Participants will be expected to pick up the pecans/gift card monthly at the diet center on campus. Participants will remain in their vehicle and a staff member from the Metabolic Diet Center will bring pecans/gift cards Compliance monitoring will also be conducted at this appointment. At the beginning and end of the diet period, data collection (described above) will occur.

Total time for study visits, after the initial screening is approximately 3 hours. Times may vary and females will require an additional 5 minutes for a urine pregnancy test a baseline and the end of the diet period. The following is an estimate of the amount of time participants will spend in study activities:

Screening appointment:

Day 1: Forms, blood pressure, weight, height, waist circumference, blood draw – 45-60 minutes

(pregnancy testing: females only – 5 minutes)

Beginning of treatment period:
Day 1: blood draw, weight, waist circumference, vascular testing– 60 minutes

(pregnancy testing: females only – 5 minutes)

Day 2: blood draw, vascular testing – 45 minutes

End of treatment period (week 12):
Day 1: blood draw, weight, waist circumference, vascular testing– 60 minutes

(pregnancy testing: females only – 5 minutes)

Day 2: blood draw, vascular testing – 45 minutes

Picking up food/gift card, fecal collections, and completing 24-hour diet recalls: ~ 7 hours

Total time for clinic and diet center visits from the beginning to the end of the study ~12 hours

8.0 Number of Subjects and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

A sample size of 128 (64 per group) is needed. To complete 128 individuals, approximately 140 participants will be recruited to account for an anticipated ~10% dropout rate.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

Power analysis for the primary endpoint, FMD, is based on the differences reported in clinical trials of tree nuts (5-8). To detect a 1.2% (standard deviation 2.4; effect size 0.5) between-condition mean difference with 80% power (α=0.05), 128 or 64 people per group are needed.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

The normality of the data will be tested before performing analyses, and transformations will be made if needed. In the primary analyses, the change in outcome measures (baseline to 12 weeks) will be compared between groups after adjustment for baseline value, age, sex, and BMI. The mixed model

procedure will be used (SAS) with randomization as a fixed factor, and baseline value for the outcome measure, age, sex, and BMI included as covariates.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Not applicable

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Not applicable

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

Not applicable

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Not applicable

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Not applicable

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Not applicable

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Not applicable

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Not applicable

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

Gastrointestinal symptoms:
Some participants may experience GI (stomach) upset from the changes to their diet with incorporation of the pecans; symptoms may include, but are not limited to, any of the following: constipation/diarrhea, nausea, and bloating. This will likely subside once the participant becomes accustomed to the study food.

Food Allergies:
Individuals will be asked to report any food allergies during the telephone screen, however it is possible that an unknown food allergy may manifest during the study. This is most likely to occur within the first week of the treatment period. Each day participants will be asked to complete a daily monitoring form so that we may track any adverse events, including potential food allergies, and identify the source as soon as possible. In addition, we ask participants to please inform study staff immediately should any adverse events occur.

Food Preparation

Pecans and meals (i.e., chicken, steamed broccoli, and roasted potatoes OR black bean quesadilla and steamed broccoli) are prepared by a chef with decades of experience who adheres to food safety protocols. There is a possibility of foodborne illness or cross contamination, but risks will be minimized by proper food handling, handwashing, and cleaning procedures. Participants are instructed to refrigerate meals immediately after leaving the clinic. If participants do not comply, this could result in foodborne illness. However, it is possible that incorrect food handling during shipping, storage or preparation, if not detected, could result in food-borne illness. Every

effort will be made to safeguard against this possibility.

Blood Sampling:
Blood draws often cause mild pain, swelling or bleeding. There may be some bruising (blood under the surface of the skin), which can be minimized by pressing on the site after the needle is removed. There is also a slight chance of infection, dizziness or fainting. These risks will be minimized and most likely eliminated by having trained staff draw the blood in a clinical setting using sterile supplies. If dizziness or fainting occurs, the symptoms will be alleviated by having the participant lie flat with their feet raised. If these should occur, the participant may be asked to remain at the clinic until the nurses have checked the participant's blood pressure and are sure the participant is ok to leave.

FMD:
There are no known risks associated with ultrasound. However, because the blood pressure cuff on the participants' right forearm is inflated tightly, it is likely that the hand and arm below the blood pressure cuff will experience "pins and needles" (tingling and pricking sensations) while the cuff is inflated and for a few minutes after it is released. During the 5 minutes that the blood pressure cuff is inflated on the forearm, the arm could become numb. This might be moderately painful. However, any discomfort or numbness should go away within minutes of cuff deflation and there are no known long-term risks associated with this test. There is a possibility for red blotching or mild bruising (petechiae) appearing on the skin above and below the location of the blood pressure cuff. Studies indicate that petechiae are rare (occurring in less than ½ of 1% of patients) and it is typically not uncomfortable and it does not require treatment. There are no risks associated with measurement of blood pressure, heart rate, or EKG as long as the participant is not allergic to adhesive tape. Temporary redness at the site of the electrode placement is possible.

SphygmoCor (Pulse Wave Analysis and Pulse Wave Velocity):
There are no known risks associated with these measurements. The sensation of pressure from the blood pressure cuff or hand-held probe may be uncomfortable. There is a possibility for red blotching or mild bruising (petechiae) appearing on the skin above and below the location of the blood pressure cuff. Studies indicate that petechiae are rare (occurring in less than ½ of 1% of patients) and it is typically not uncomfortable and does not require treatment.

Loss of Confidentiality:
There is always a potential for loss of confidentiality despite our best efforts. To prevent this from occurring all records are coded with a unique ID number and no names are used. Records containing names or other identifying information are kept under lock at the PI's research office. All records associated with an individual's participation in the study will be subject to the usual confidentiality standards applicable to medical records. In the event of publication of this research, no personal identifying information will be disclosed.

Fecal Sample Collection:
Some participants may experience a certain level of embarrassment or discomfort from being asked to collect stool samples.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 13.0.

Participants will receive their screening laboratory results, including a complete blood count, HbA1C and blood lipid values, at no cost.

11.2 Potential Benefits to Others

Include benefits to society or others.

The findings of this study will be applicable to the approximately, 50% of Americans are at risk for CVD (29). If shown to improve peripheral vascular assessments, lipid and lipoprotein profile and glycemic control compared to usual average American intake, this may provide evidence in favor of incorporating pecans. As approximately one-third of deaths are caused by cardiovascular disease and events, this could be helpful to those at risk. The findings of this research will be published in peer reviewed journals and these papers will likely be cited by clinical management guidelines and inform dietary recommendations. Therefore, the findings of this research are likely to inform clinical practice and dietary guidelines for individuals who have an elevated risk of cardiovascular disease (overweight or obese BMI and at least one symptom of metabolic syndrome).

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Screening results will be provided to all potential participants (regardless of their eligibility status) within 2 weeks of their screening appointment. All screening results will be reviewed by the Nurse Practitioner or Physician at the Clinical Center. Should any abnormal lab values be identified that warrant further evaluation the individual will be contacted (by the Study Coordinator) and asked to schedule a visit with their primary care physician. At the completion of the study, the key findings from the study overall will be posted on our laboratory's website (https://hhd.psu.edu/nutrition/cardiometabolic-lab). Upon request, individual results may be given to participants at the completion of all study related data collection and analyses.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

For their time and participation in the study participants will receive monetary compensation of up to $200 (check or direct deposit). For participants who withdraw from the study, compensation will be prorated as follows and paid at the completion of their participation in the study:

Completion of day 1 and day 2 testing at baseline = $50
Completion of three 24-hour recalls at baseline= $25
Completion of three 24-hour recalls at week 6 = $25
Completion of day 1 and day 2 testing at 12 weeks = $75
Completion of three 24-hour recalls at week 12 = $25

Payments will be made at the completion of a participant's involvement with the study.

Participants may not be eligible for compensation if determined that specific work or visa laws conflict.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

The participants will not bear any costs due to their participation in the study.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

Not applicable – the research does not involve more than minimal risk.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Penn State University Clinical Research Center -The clinical aspects of this study will be conducted at the Clinical Research Centre (CRC) on the University Park campus of the Pennsylvania State University. The CRC is a purpose-built research unit that supports human clinical research trials, and is fully equipped with exam rooms, invasive and general procedure rooms and five hospital-style bedrooms with bathrooms. There is also a specimen processing room with refrigerated and unrefrigerated centrifuges for preparation of samples. The study investigators will work closely with experienced CRC staff (physicians, nurse practitioners, registered nurses and research technologists) to optimize and facilitate

the research protocol. The principal investigators, co-investigator, and project coordinators are experienced with conducting research at this location and have conducted multiple clinical trials at this location previously.

The Penn State Metabolic Diet Study Center is a state-of-the-art facility consisting of a spacious dining area, a pantry and a fully-equipped kitchen specifically designed for nutrition studies. In addition, this area is available for small group meetings with study participants and counseling/information exchange with small groups of individuals.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

Given the wide age range and broad recruitment criteria we believe these methods, which have been successful in the past, will enable us to recruit the necessary participants within the appropriate time frame.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

The Principal Investigators will be responsible for assuring through personal contact between the co-investigator, clinical staff and coordinators that each individual clearly understands and accepts the obligations incurred in the undertaking of this clinical trial.

The Principal Investigators will ensure that the clinical staff fully understand the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with the applicable federal regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Nursing staff are always present during clinical testing. Highly trained nursing staff will perform clinical assessments. Should an individual require psychological services they will be referred to the on-campus clinic: Psychological Clinic, 314 Moore Bldg., University Park, Phone: 865-2191.

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

All study staff will be required to complete the Human Participant Training and Bloodborne Pathogen Training as mandated by the Pennsylvania State University Office of Research Protections. In addition, as part of the initial training for this study, all staff members (e.g. project managers, research coordinators, assistants, and Clinical Research Center [CRC] nursing staff) will conduct an initial project start-up meeting to review the scientific protocol and ensure all study procedures are in place.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

IBC approval will be obtained for the collection and analysis of blood and fecal samples.

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☒ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

☐ St. Joseph Administrative Review – **Penn State Health only** – Penn State Health Research that will be conducted at St. Joseph Medical Center or St. Joseph Community Medical Groups.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable

18.0 Adverse Event Reporting

18.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Auditing and Inspecting

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

Blood (serum/plasma) may be stored for future testing.

Fecal samples will be stored for future testing of microbial composition or identification of metabolites.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Chandlee Lab: Room 318 in a locked -80^{o} degree freezer

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

Specimens will be destroyed 3 years after publication of results, unless permission has been granted to keep. If permission to keep the samples has been granted, the samples may be stored indefinitely or until the integrity of the sample is comprised; these samples will be stored with non-identifiable labels.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Specimens will be boxed, labeled by sample type, study name, and subject ID, and stored in a locked -80^{o} degree freezer. Samples will only be accessible to designated staff and students for purposes outlined in this proposal.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

All specimens will be coded with non-identifiable labels. Participants may elect to make their samples available for additional analyses by study collaborators.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

No results about the use of data or specimens are returned to participants. The samples are labeled with non-identifiable labels and after the list linking identifiers to the codes has been destroyed it will not be possible to identify individuals.

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

References:

1. U.S. Department of Agriculture, Agricultural Research Service. 2016. Nutrient Intakes from Food and Beverages: Mean Amounts Consumed per Individual, by Gender and Age, What We Eat in America, NHANES 2013-2014.
2. Bowman SA CJ, Friday JE, Lynch KL, LaComb RP, Moshfegh AJ. Food Patterns Equivalents Intakes by Americans: What We Eat in America, NHANES 2003-04 and 2013-14 Dietary Data Brief No. 17. 2017.
3. Dietary Guidelines Advisory Committee. Scientific report of the 2015 dietary guidelines advisory committee. Washington (DC): USDA and US Department of Health and Human Services 2015.
4. U.S. Department of Health and Human Services. 2015-2020 Dietary Guidelines for Americans. Office of Disease Prevention and Health Promotion, 2016.
5. Rebholz CM, Appel LJ. Health effects of dietary patterns: critically important but vastly understudied. Am J Clin Nutr 2018;108:207-208.
6. Ros E. Nuts and CVD. Br J Nutr 2015;113 Suppl 2:S111-20.
7. Gu L, Kelm MA, Hammerstone JF, Beecher G, Holden J, Haytowitz D, Gebhardt S, Prior RL. Concentrations of Proanthocyanidins in Common Foods and Estimations of Normal Consumption. The Journal of Nutrition 2004;134:613-617.
8. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. The American Journal of Clinical Nutrition 2012.

9. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. Journal of the American Heart Association 2015;4.
10. Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, Heussen N, Gross HB, Keen CL, Schroeter H, Kelm M. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. J Am Coll Cardiol 2008;51:2141-9.
11. Casas-Agustench P, Lopez-Uriarte P, Ros E, Bullo M, Salas-Salvado J. Nuts, hypertension and endothelial function. Nutr Metab Cardiovasc Dis 2011;21 Suppl 1:S21-33.
12. Neale EP, Tapsell LC, Guan V, Batterham MJ. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7:e016863.
13. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. The American Journal of Clinical Nutrition 2015;102:1347-1356.
14. Tindall A, Johnston E, Kris-Etherton P, Petersen K. The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2019;109:297–314.
15. Viguiliouk E, Kendall CW, Blanco Mejia S, Cozma AI, Ha V, Mirrahimi A, Jayalath VH, Augustin LS, Chiavaroli L, Leiter LA, de Souza RJ, Jenkins DJ, Sievenpiper JL. Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. PLoS ONE 2014;9:e103376.
16. Morgan WA, Clayshulte BJ. Pecans lower low density lipoprotein cholesterol in people with normal lipid levels. Journal of the American Dietetic Association 2000;100:312-318.
17. Rajaram S, Burke K, Connell B, Myint T, Sabaté J. A monounsaturated fatty acid–rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. The Journal of Nutrition 2001;131:2275-2279.
18. McKay DL, Eliasziw M, Chen CYO, Blumberg JB. A Pecan-Rich Diet Improves Cardiometabolic Risk Factors in Overweight and Obese Adults: A Randomized Controlled Trial. Nutrients 2018;10.
19. Hudthagosol C, Haddad EH, McCarthy K, Wang P, Oda K, Sabate J. Pecans acutely increase plasma postprandial antioxidant capacity and catechins and decrease LDL oxidation in humans. J Nutr 2011;141.
20. Wang L, Bordi PL, Fleming JA, Hill AM, Kris-Etherton PM. Effect of a Moderate Fat Diet With and Without Avocados on Lipoprotein Particle Number, Size and Subclasses in Overweight and Obese Adults: A Randomized, Controlled Trial. Journal of the American Heart Association 2015;4:e001355.
21. Tindall AM, Petersen KS, Skulas-Ray AC, Richter CK, Proctor DN, Kris-Etherton PM. Replacing Saturated Fat With Walnuts or Vegetable Oils Improves Central Blood Pressure and Serum Lipids in Adults at Risk for Cardiovascular Disease: A Randomized Controlled-Feeding Trial. J Am Heart Assoc 2019;8:e011512.
22. Lassale C, Tzoulaki I, Moons KGM, Sweeting M, Boer J, Johnson L, Huerta JM, Agnoli C, Freisling H, Weiderpass E, Wennberg P, van der A DL, Arriola L, Benetou V, Boeing H, Bonnet F, Colorado-Yohar SM, Engström G, Eriksen AK, Ferrari P, Grioni S, Johansson M, Kaaks R, Katsoulis M, Katzke V, Key TJ, Matullo G, Melander O, Molina-Portillo E, Moreno-Iribas C, Norberg M, Overvad K, Panico S, Quirós JR, Saieva C, Skeie G, Steffen A, Stepien M, Tjønneland A, Trichopoulou A, Tumino R, van der Schouw YT, Verschuren WMM, Langenberg C, Di Angelantonio E, Riboli E, Wareham NJ, Danesh J, Butterworth AS. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. European Heart Journal 2017:ehx448-ehx448.
23. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis. Hypertension 2016;67:183-90.
24. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Hansen TW, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 2014;63:636-46.

25. Ma Y, Njike VY, Millet J, Dutta S, Doughty K, Treu JA, Katz DL. Effects of walnut consumption on endothelial function in type 2 diabetic subjects: a randomized controlled crossover trial. Diabetes Care 2010;33:227-232.
26. Ros E, Nunez I, Perez-Heras A, Serra M, Gilabert R, Casals E, Deulofeu R. A walnut diet improves endothelial function in hypercholesterolemic subjects: a randomized crossover trial. Circulation 2004;109.
27. Sari I, Baltaci Y, Bagci C, Davutoglu V, Erel O, Celik H, Ozer O, Aksoy N, Aksoy M. Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: a prospective study. Nutrition 2010;26:399-404.
28. Chen C-YO, Holbrook M, Duess M-A, Dohadwala MM, Hamburg NM, Asztalos BF, Milbury PE, Blumberg JB, Vita JA. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, cross-over trial. Nutrition Journal 2015;14:1-11.
29. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019;139:e56-e66.

22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form."

Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data," which is available on the IRB's website. In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all sub-sections of section 22.

For all other research: complete the following section. Please refer to PSU Policy AD95 for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State's Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.

22.1 Which of the following identifiers will be recorded for the research project? Check all that apply. If none of the following identifiers will be recorded, do not check any of the boxes.

	Hard Copy Data	Electronic Stored Data
Names and/or initials (including on signed consent documents)	☒	☒

All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes,	☒	☒
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older	☒	☒
Telephone numbers	☒	☒
Fax numbers	☐	☐
Electronic mail addresses	☒	☒
Social security numbers	☐	☐
Medical record numbers	☐	☐
Health plan beneficiary numbers	☐	☐
Account numbers	☐	☐
Certificate/license numbers	☐	☐
Vehicle identifiers and serial numbers, including license plate numbers	☐	☐
Device identifiers and serial numbers	☐	☐
Web Universal Resource Locators (URLs)	☐	☐
Internet Protocol (IP) address numbers	☒	☐
Biometric identifiers, including finger and voice prints	☐	☐
Full face photographic images and any comparable images	☐	☐
Any other unique identifying number, characteristic, or code (such as the pathology number)	☐	☐
Study code number with linking list	☐	☒
Genomic sequence data	☐	☐
State ID numbers	☐	☐
Passport numbers	☐	☐
Driver's license numbers	☐	☐

22.2 If storing paper records of research data, answer the following questions:

22.2.1 Where will the paper records, including copies of signed consent forms, associated with this research study will be stored?

Consent forms and data collections sheets will be stored in a locked filing cabinet in a locked office (317 Chandlee Laboratory) and in the Clinical Research Centre, Noll Laboratory. Medical history forms will only be stored in paper form in locked filling cabinets in 317 Chandlee Laboratory and in the Clinical Research Centre, Noll Laboratory.

22.2.2 How will the paper records be secured?

Paper recorded will be secured in a locked filing cabinet in a locked office. Only research personnel have access to the filing cabinet.

22.2.3 How will access to the paper records be restricted to authorized project personnel?

Only authorized project personnel will have key access to the locked filing cabinets.

22.3 If storing electronic records of research data, indicate where the electronic data associated with this research study will be stored. Check all that apply.

☒ Penn State-provided database application. Check which of the following database applications are being used (check all that apply):

☐ Penn State REDCap

☒ Other – Specify - provided and approved database application:

OneDrive

☐ Penn State, College, or Department IT file server
☐ Box.psu.edu (To be retired Sept. 2021; see https://storage.psu.edu/)
☐ Web-based system provided by the sponsor or cooperative group - Specify URL and contact information:

☐ Other – Specify the database application or server:

Provide details about the data security features or attach security documentation provided by sponsor or group:

If there is a list/key that links indirect identifiers (code numbers, participant IDs, etc.) to direct identifiers, that list must not be comingled (i.e., stored in the same location) as the identifiable data, including copies of signed informed consent forms. Additionally, access to that list/key must be restricted to authorized project personnel.

22.4 Is there a list/key that links code numbers to identifiers?

☒ Yes - explain how the list that links the code to identifiers is stored separately from coded data:
A master list containing a study ID number and participant's identity will be used. This file will be stored in a folder saved to OneDrive where only approved study personnel will be able to access it through their OneDrive account. No data containing study ID#'s (code numbers) will be stored with the master list. Upon completion of data collection, only the investigators and study coordinator will have access to the list. This list will be deleted 3 years after publication of the study results.
☐ Not applicable, there is no list that links code numbers to identifiers. Skip to section 22.6.

22.5 Is there a list of people who have access to the list/key?

☒ Yes – explain how access to that list is restricted and why certain persons require access.
The principal investigator, co-investigator, study coordinators and trained study personnel will have access to data and specimens. These personnel will have access to the list because they will be directly involved with the study participants and therefore need access to identifying information in the course of participant management.

☐ No – explain why not:

22.6 Describe the mechanism in place to ensure only approved research personnel have access to the stored research data (electronic and paper).

☒ Password-protected files
☐ Role-based security
☐ Specify all other mechanisms used to ensure only permitted users have access to the stored research data.
Paper files are stored under lock and key.

The use of mobile devices or wireless activity trackers to collect identifiable research data must be approved by the Office of Information Security. Before completing this section, please contact security@psu.edu to confirm approval.

22.7 Will any research data (such as survey data) be collected on a mobile device, such as an electronic tablet, cell phone, or wireless activity tracker?

☒ No
☐ Yes - answer the following questions:

22.7.1 Specify the provider of the mobile devices(s)

☐ Supplied by the sponsor
☐ Penn State owned device
☐ A personal device
☐ Other – Please specify source:

22.7.2 Specify the type(s) of mobile device(s) that will be used to capture data and all identifiers captured on the mobile device(s). Please list all devices, and if more than one, the identifiers to be collected on each.

22.7.3 Specify the type of data collected on the mobile devices(s).

22.7.4 Specify the application or website used to collect the data from the mobile device, if applicable.

22.7.5 Describe the measures taken to protect the confidentiality of the data collected on mobile device(s). Please address physical security of the device(s), electronic security, and secure transfer of data from device(s) to the previously indicated data/file storage location provided in section 22.3.

The use of online survey tools and email to collect or send research data containing identifiers that represent more than minimal risk to subjects must be approved by the Office of Information Security. Before completing this section, please contact security@psu.edu.

22.8 Will any research data be directly entered/sent by subjects over the internet or via email (e.g., data capture using on-line surveys/questionnaires, surveys via email, observation of chat rooms or blogs)?

☐ No
☒ Yes - answer the following questions:

22.8.1 Specify the identifiers collected over the internet or via email (Including IP addresses if IP addresses will be collected).

The ASA24 system does not collect any identifying data directly from Respondents. However, IP address information is accessed for the purpose of routing information between the server and the respondent's computer—often the IP address is that of the user's Internet Service Provider (ISP). IP addresses are not stored or tracked by the ASA24 system. However, logs of connections are kept in the hosting environment for audit trail purposes. This information is not mined in any way but would be available if there were a legal obligation to release it.

22.8.2 Specify the type of data collected over the internet or via email.

Intake of foods, beverages and supplements in the past 24 hours. All subjects are provided with a unique personal link that aligns with their study ID for completion of the survey so no identifying information is collected.

22.8.3 Describe the measures taken to protect the confidentiality of the data collected?

All subjects are provided will a unique personal link that aligns with their study ID that they use to access the survey. No identifying information is uploaded to the website or collected from the subject.

22.8.4 Describe how the research team will access the data once data collection is complete.

Response data are secured at the hosting site using industry standard security controls, including firewalls and encryption. All data entered into the ASA24 system at the Respondent's computer is encrypted by the internet browser (e.g., Internet Explorer, Firefox) before they are transmitted to our servers using Secure Socket Layer (SSL) Technology. SSL allows for the authentication of the sending and receiving computers.

Only approved study members and the ASA24 operations team can access response data. Access is gained through the Researcher Portal, which is username and strong password protected. Data are downloaded in spreadsheets directly from the Researcher Portal.

22.8.5 If the research involves online surveys, list the name(s) of the service provider(s) that will be used for the survey(s) (e.g., REDCap, Penn State licensed Qualtrics, Survey Monkey, Zoomerang)? (Note: The IRB strongly recommends the use of REDCap for online surveys that obtain sensitive identifiable human subjects data.)

☐ Penn State REDCap
☐ Penn State Qualtrics (de-identified data only)
☒ Other - Please specify:
Application: National Cancer Institute ASA-24
URL (If applicable): https://epi.grants.cancer.gov/asa24/

22.8.6 If the answer above is "Other" contact security@psu.edu for approval of an alternative data capture method

Depending on the nature of the subject matter involved, certain security requirements must be in place for the audio and/or video recording or photographing of subjects. If the subject matter presents more than minimal risk to the subjects, then, before completing the section below, please contact the Office of Information Security at security@psu.edu to confirm whether these requirements are required.

22.9 Will any type of recordings (e.g., audio or video) or photographs of the subjects be made during this study?

☒ No - skip to section 22.10
☐ Yes - answer the following questions:

22.9.1 What will be used to capture the audio/video/images? Give a brief description of content.

☐ Audio – Describe the intended content of the audio recording:

☐ Video – Describe the intended content of the video recording:

☐ Photographs of the subjects – Describe the intended content of the photographs:

☐ 3-D Images – Describe the intended content of the of 3-D images:

☐ Other - Specify:

22.9.2 How will the recordings/photographs/images be stored (electronically or physically)?

22.9.3 Where will the recordings/photographs/images be stored?

22.9.4 Who will have access to the recordings/photographs/images?

22.9.5 Will any of the recordings be transcribed?

☐ Not applicable
☐ No
☐ Yes – indicate who will be doing the transcribing?

22.9.6 Will the recordings/photographs be used for purposes other than this research study?

☐ No
☐ Yes - specify purpose(s) (e.g., publication, presentations, educational training, future undetermined research):

22.10 Certificate of Confidentiality (COC) - Is the research biomedical, behavioral, clinical or other research that is funded by the National Institutes of Health (NIH)?

☐ Yes - check one of the following:

- ☐ The research involves human subjects as defined by the DHHS regulations (See Worksheet HRP-310).
- ☐ The research involves collecting or using biospecimens that are identifiable to an individual.
- ☐ If collecting or using biospecimens as part of the research, there is a small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual.
- ☐ The research involves the generation of individual level, human genomic data.

Note: If <u>any</u> of the 4 items above are checked, a COC is automatically issued by NIH and applies to the research. Information about the COC must be included in the consent form.

☒ No - answer the following question.

If the research is not funded by NIH, will the investigator apply for a COC for this research study?

☒ No
☐ Yes

Note: For research not funded by NIH, the IRB may require a COC if the research is collecting personally identifiable information and the information is sensitive and/or the research is collecting information that if disclosed could significantly harm or damage the subject.

22.11 What steps will be taken to protect subjects' privacy interests? (Check all that apply.)

- ☒ Identification and recruitment of potential subjects follows procedures consistent with privacy standards
- ☒ Consent discussion and research interventions will take place in a private setting
- ☒ Limiting the information being collected to only the minimum amount of data necessary to accomplish the research purposes
- ☒ Limiting the people with access to the identifiable research data to the minimum necessary as specified in the application and consent process
- ☐ Other – Specify:

22.12 What is the process for ensuring correctness of data entry?

- ☐ Double data entry to reduce risk of errors
- ☒ Electronic edit checks to ensure data being entered are not obviously incorrect
- ☒ Random internal quality and assurance checking of research data
- ☒ Direct entry by subjects
- ☐ Other - Specify:

22.13 Does this research involve the generation of large-scale human genomic data as defined in NIH Genomic Data Sharing Policy (http://gds.nih.gov)?

- ☒ No
- ☐ Yes – If Yes, describe the plan for de-identifying the dataset before sharing it with NIH-designated data repositories.

22.14 The European Union (EU) General Data Protection Regulation (GDPR)

22.14.1 To determine if the research is subject to the GDPR answer the following questions:

22.14.1.1 Will the Penn State principal investigator, or another entity under the Penn State principal investigator's direction, be collecting, recording, storing, using, any personal data* of any subjects physically located in the European Economic Area (EEA) at the time of data collection (even if the subject is NOT an EEA resident) or any EEA citizens? (This includes recruitment through social media sites, use of third party internet sites, mobile devices or apps to collect data, and/or direct receipt of data from subjects.)**

- ☒ No
- ☐ Yes (This research may be subject to the GDPR)

22.14.1.2 Does this research involve the transfer of personal data collected under the GDPR from an EEA country? (This includes direct transfer of data from research collaborators.)

- ☒ No
- ☐ Yes (This research may be subject to the GDPR)

22.14.2 If the research may be subject to the GDPR as indicated in the answers to the questions above, answer the following:

22.14.2.1 Will any of the data fall into one of the following categories: health data, racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, genetic data, biometric data used for purpose of identifying an individual, sex life or sexual orientation?

☐ No
☐ Yes

22.14.2.2 Will any of the data be related to criminal convictions or offenses?

☐ No
☐ Yes

Comments on any of the above responses:

* "Personal data" means any information relating to an identified or identifiable natural person; an identifiable natural person is one who can be identified, directly or indirectly, by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

** European Economic Area (EEA) – Includes the 28-member states of the European Union (Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia Spain, Sweden, UK) and Norway, Iceland, Lichtenstein.

22.15 Does this research involve transfer or disclosure of data and/or specimens to and/or from Penn State?

☐ No - skip the remainder of section 22.15.
☒ Yes - answer the following questions.

Check all that apply:

☒ **Data** are being transferred or disclosed **to** Penn State

What is the name of the third party(ies) (the institution, sponsor, etc.) sending or providing the data?

LabCorp (Morrisville, NC)
Quest Diagnostics (Pittsburgh, PA)

Is the third party requiring us to sign a contract regarding the data?

☐ Yes - If Yes, this contract must go through the Office of Sponsored Programs
https://www.research.psu.edu/osp/overview-pages/data-use-agreements

☒ No

☐ **Data** are being transferred or disclosed **from** Penn State

What is the name(s) of the third party(ies) (the institution, sponsor, etc.) receiving or accessing the data?

Note: Data transfers or disclosures may require a Data Use Agreement (DUA).

☐ **Specimens** are being transferred **to** Penn State

What is the name(s) of the third party(ies) (the institution, sponsor, etc.) sending the specimens?

☒ **Specimens** are being transferred **from** Penn State
What is the name(s) of the third party(ies) (the institution, sponsor, etc.) receiving the specimens?
LabCorp and Quest Diagnostics

Note: All material transfers, either sending or receiving, require a Material Transfer Agreement (MTA). Please contact the Office of Technology Management for more information.

22.15.1 Describe how the data/specimens will be securely transferred or disclosed to/from the third party(ies).

LabCorp and Quest Diagnostics

Serum/plasma samples will be shipped to Quest on dry ice via FedEx or a Quest Courier. The Blood samples will be labeled with the subjects study ID number and the timepoint of collection; no other information will be on the vial.

22.15.2 How are the research data/specimens being transferred from and/or sent to the third party(ies)? Complete the appropriate section(s) and check all that apply within each completed section.

22.15.2.1 Data being transferred or disclosed **to** Penn State**:**

- ☐ Data are being received in aggregate/metrics (just counts, no individual data)
- ☐ De-identified individual data are being received and there is no linking list at either institution (no identifiers, or links to identifiers, such as code numbers)
- ☐ Coded research data without any identifiers are being received and the linking list remains with the entity sending the data; the recipient of the data will not have access to the linking list
- ☐ Coded research data with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3 aside from Study Code) are being received and the linking list remains with the entity sending the data; the recipient of the data will not have access to the linking list
- ☐ Data with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3) are being received and the linking list remains with the entity sending the data; the recipient of the data will have access to the linking list
- ☐ Data with identifiers along with the linking list are being received
- ☒ Other – Specify:

Data with only the Study ID are being received by PSU. The linking list remains with the PSU; the entity sending the data will not have access to the linking list

22.15.2.2 Data being transferred or disclosed **from** Penn State**:**

- ☐ Data are being sent in aggregate/metrics (just counts, no individual data)
- ☐ De-identified individual data are being sent and there is no linking list at either institution (no identifiers, or links to identifiers, such as code numbers)

☐ Coded research data without any identifiers are being sent and the linking list remains with the entity sending the data; the recipient of the data will not have access to the linking list
☐ Coded research data with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3 aside from Study Code) are being sent and the linking list remains with the entity sending the data; the recipient of the data will not have access to the linking list
☐ Data with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3) are being sent and the linking list remains with the entity sending the data; the recipient of the data will have access to the linking list
☐ Data with identifiers along with the linking list are being sent
☐ Other – Specify:

22.15.2.3 Specimens being transferred or disclosed **to** Penn State**:**

☐ De-identified specimens are being received and there is no linking list at either institution (no identifiers, or links to identifiers, such as code numbers)
☐ Coded specimens without any identifiers are being received and the linking list remains with the entity sending the specimens; the recipient of the specimens will not have access to the linking list
☐ Coded specimens with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3 aside from Study Code) are being received and the linking list remains with the entity sending the specimens; the recipient of the specimens will not have access to the linking list
☐ Coded specimens with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3) are being received and the linking list remains with the entity sending the specimens; the recipient of the specimens will have access to the linking list
☐ Coded specimens with identifiers along with the linking list are being received
☐ Other – Specify:

22.15.2.4 Specimens being transferred or disclosed **from** Penn State**:**

☐ De-identified specimens are being sent and there is no linking list at either institution (no identifiers, or links to identifiers, such as code numbers)
☒ Coded specimens without any identifiers are being sent and the linking list remains with the entity sending the specimens; the recipient of the specimens will not have access to the linking list
☐ Coded specimens with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3 aside from Study Code) are being sent and the linking list remains with the entity sending the specimens; the recipient of the specimens will not have access to the linking list
☐ Coded specimens with identifiers (such as dates and/or any of the identifiers listed in section 22.15.3) are being sent and the linking list

remains with the entity sending the specimens; the recipient of the specimens will have access to the linking list

☐ Coded specimens with identifiers along with the linking list are being sent

☐ Other – Specify:

22.15.3 If transferring data/specimens with identifiers to or from Penn State, which of the following identifiers will be included with the data/specimens? Check all that apply:

☐ Names	☐ Medical record numbers
☐ Initials	☐ Health plan beneficiary numbers
☐ Street address	☐ Account numbers
☐ City	☐ Certificate/license numbers
☐ Driver's License numbers	☐ Passport numbers
☐ State	☐ State ID numbers
☐ Zip Codes	☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ County	☐ Device identifiers and serial numbers
☐ Geocodes	☐ Web Universal Resource Locators (URLs)
☐ Precincts	☐ Internet Protocol (IP) address numbers
☐ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death	☐ Biometric identifiers, including finger and voice prints
☐ Ages > 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older	☐ Full face photographic images and any comparable images
☐ Telephone numbers	☐ Any other unique identifying number, characteristic, or code (such as the pathology number) Specify:
☐ Fax numbers	☒ Study code numbers
☐ Electronic mail addresses	☐ Master list linking study code numbers to subject(s)
☐ Social security numbers	☐ Genomic sequence data
	☐ Other – specify:

Balzer, J., Rassaf, T., Heiss, C., Kleinbongard, P., Lauer, T., Merx, M., . . . Kelm, M. (2008). Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J Am Coll Cardiol, 51*(22), 2141-2149. doi:10.1016/j.jacc.2008.01.059

Casas-Agustench, P., Lopez-Uriarte, P., Ros, E., Bullo, M., & Salas-Salvado, J. (2011). Nuts, hypertension and endothelial function. *Nutr Metab Cardiovasc Dis, 21 Suppl 1*, S21-33. doi:10.1016/j.numecd.2011.01.009

Del Gobbo, L. C., Falk, M. C., Feldman, R., Lewis, K., & Mozaffarian, D. (2015). Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. *The American Journal of Clinical Nutrition, 102*(6), 1347-1356. doi:10.3945/ajcn.115.110965

Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., . . . Prior, R. L. (2004). Concentrations of Proanthocyanidins in Common Foods and Estimations of Normal Consumption. *The Journal of Nutrition, 134*(3), 613-617. Retrieved from http://jn.nutrition.org/content/134/3/613.abstract

Hooper, L., Kay, C., Abdelhamid, A., Kroon, P. A., Cohn, J. S., Rimm, E. B., & Cassidy, A. (2012). Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. *The American Journal of Clinical Nutrition*. doi:10.3945/ajcn.111.023457

Hudthagosol, C., Haddad, E. H., McCarthy, K., Wang, P., Oda, K., & Sabate, J. (2011). Pecans acutely increase plasma postprandial antioxidant capacity and catechins and decrease LDL oxidation in humans. *J Nutr, 141*. doi:10.3945/jn.110.121269

Matsuzawa, Y., Kwon, T. G., Lennon, R. J., Lerman, L. O., & Lerman, A. (2015). Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association, 4*(11). doi:10.1161/jaha.115.002270

McKay, D. L., Eliasziw, M., Chen, C. Y. O., & Blumberg, J. B. (2018). A Pecan-Rich Diet Improves Cardiometabolic Risk Factors in Overweight and Obese Adults: A Randomized Controlled Trial. *Nutrients, 10*(3). doi:10.3390/nu10030339

Morgan, W. A., & Clayshulte, B. J. (2000). Pecans lower low density lipoprotein cholesterol in people with normal lipid levels. *Journal of the American Dietetic Association, 100*(3), 312-318.

Neale, E. P., Tapsell, L. C., Guan, V., & Batterham, M. J. (2017). The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open, 7*(11), e016863. doi:10.1136/bmjopen-2017-016863

Rajaram, S., Burke, K., Connell, B., Myint, T., & Sabaté, J. (2001). A monounsaturated fatty acid–rich pecan-enriched diet favorably alters the serum lipid profile of healthy men and women. *The Journal of Nutrition, 131*(9), 2275-2279.

Ros, E. (2015). Nuts and CVD. *Br J Nutr, 113 Suppl 2*, S111-120. doi:10.1017/s0007114514003924

Tindall, A., Johnston, E., Kris-Etherton, P., & Petersen, K. (2019). The effect of nuts on markers of glycemic control: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr, 109*, 297–314.

Tindall, A. M., Petersen, K. S., Skulas-Ray, A. C., Richter, C. K., Proctor, D. N., & Kris-Etherton, P. M. (2019). Replacing Saturated Fat With Walnuts or Vegetable Oils Improves Central Blood Pressure and Serum Lipids in Adults at Risk for Cardiovascular Disease: A Randomized Controlled-Feeding Trial. *J Am Heart Assoc, 8*(9), e011512. doi:10.1161/jaha.118.011512

U.S. Department of Health and Human Services. (2016). *2015-2020 Dietary Guidelines for Americans*. Office of Disease Prevention and Health Promotion

Viguiliouk, E., Kendall, C. W., Blanco Mejia, S., Cozma, A. I., Ha, V., Mirrahimi, A., . . . Sievenpiper, J. L. (2014). Effect of tree nuts on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled dietary trials. *PLoS ONE, 9*(7), e103376. doi:10.1371/journal.pone.0103376

Wang, L., Bordi, P. L., Fleming, J. A., Hill, A. M., & Kris-Etherton, P. M. (2015). Effect of a Moderate Fat Diet With and Without Avocados on Lipoprotein Particle Number, Size and Subclasses in Overweight and Obese Adults: A Randomized, Controlled Trial. *Journal of the American Heart Association, 4*(1), e001355. doi:10.1161/jaha.114.001355