

## ARIC Manuscript Proposal #4143

PC Reviewed: 10/11/22  
SC Reviewed: \_\_\_\_\_

Status: \_\_\_\_\_  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Late-life dietary intake and risk of cardiovascular disease, chronic kidney disease, and mortality in the ARIC study

**b. Abbreviated Title:** Late-life diet and CVD, CKD, and mortality

### 2. Writing Group:

Writing group members:

- Shutong Du
- Lyn Steffen
- Joe Coresh
- Casey M. Rebholz

***Others are welcome.***

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SD **[please confirm with your initials electronically or in writing]**

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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### 3. Timeline:

Data analysis and manuscript preparation is anticipated to take place within one year of approval of this proposal. We are seeking approval for this proposal now since we plan to submit an abstract based on this proposal to the ARIC Publications Committee in order to submit for AHA Epidemiology and Prevention | Lifestyle and Cardiometabolic Health Scientific Sessions 2023 (submission deadline: October 12, 2022).

#### **4. Rationale:**

Previous research has suggested that the adoption of a healthy diet may have a beneficial impact on health outcomes. A healthy diet, such as the Dietary Approaches to Stop Hypertension (DASH) diet or the Mediterranean diet, is associated with lower risk of cardiometabolic diseases.<sup>1,2</sup> On the other hand, a diet high in ultra-processed foods intake is associated with a wide range of adverse health outcomes. Ultra-processed foods are industrially made, ready to eat/heat formulations that contain artificial additives including preservatives, sweeteners or colorants, and are made entirely from industrial substances derived from foods, but with little to no intact foods.<sup>3</sup> The consumption of ultra-processed foods has been steadily increasing for the past two decades among U.S. adults and children.<sup>4,5</sup> With these types of foods becoming easily accessible in the global food supply and in the general population's diet, it is important to understand and characterize the diet across different life stages. There is extensive research on the topic of dietary habits and risk of disease among adolescents and middle aged-adults. However, less is known about diet and disease associations among older adults.

Given the fact that age-related physiological decline can impact one's nutritional status, it is important to characterize dietary intake among older adults, and to quantify the association between dietary intake and risk of chronic diseases within this specific population. We aim to describe the different aspects of diet (diet quality defined by healthy dietary patterns, ultra-processed foods intake), and quantify the association between aspects of diet and adverse health outcomes including mortality, cardiovascular disease, and chronic kidney disease.

#### **5. Main Hypothesis/Study Questions:**

##### **Specific Aim:**

1. To describe the association between diet and baseline sociodemographic, behavioral, and clinical characteristics among adults during late-life.
2. To examine associations between late-life diet and risk of clinical outcomes including all-cause mortality, cardiovascular disease, and chronic kidney disease over time.

##### **Hypothesis:**

1. We hypothesize that lower quality of dietary intake (lower adherence to healthy dietary patterns, higher intake of ultra-processed food) during late-life is associated with lower levels socioeconomic status (education), less healthy behaviors (smoking, alcohol consumption, physical activity), and higher prevalence of clinical conditions (hypertension, obesity, diabetes, chronic kidney disease, cardiovascular disease).
2. We hypothesize that lower diet quality during late-life (lower adherence to healthy dietary patterns, higher intake of ultra-processed food) is associated with a higher risk of incident cardiovascular disease, incident chronic kidney disease, and all-cause mortality.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

**Study Design:**

We will investigate the association between dietary intake and subsequent disease outcomes during late-life (mean age 71 years at the carotid MRI visit). Ultra-processed food intake and adherence scores for healthy dietary patterns will be calculated based on dietary intake data collected with a food frequency questionnaire (FFQ) at the carotid MRI visit.

**Inclusion/Exclusion Criteria:**

We will exclude participants based on following criteria:

- 1) Missing or implausible dietary data
  - a. <500 or >3500 kcal/day for women, <600 or >4500 kcal for men
  - b. Missing 10 or more items on the FFQ
  - c. Missing dietary data required to assess adherence to healthy dietary patterns
- 2) Missing covariates [age, sex, race, center, body mass index, education level as a proxy for socioeconomic status, alcohol, smoking status, physical activity level, fasting glucose, systolic blood pressure, and estimated glomerular filtration rate (eGFR)]
- 3) Non-black and non-white participants, black participants from Minneapolis, Minnesota, and black participants from Washington County, Maryland
- 4) Prevalent cases of cardiovascular disease or chronic kidney disease

**Dietary Assessment:**

Late-life diet will be assessed using dietary data collected during the carotid MRI visit. Participants were asked to provide the frequency of consumption for a particular portion of each food item in the past year. Food frequency categories ranged from less than 1 serving per month to more than 6 servings per day. Nutrient and total energy intake were calculated based on consumption frequency and nutritional content of each food item provided by US Department of Agriculture data sources.

**Classification of Ultra-Processed Food:**

All food items on the FFQ were classified into one of four categories according to the NOVA system based on processing level: 1) unprocessed or minimally processed foods, including foods obtained directly from the nature, and undergo little or no alteration other than methods such as freezing, drying or pasteurization, and with no addition of culinary ingredients; 2) processed culinary ingredients, including substances extracted from natural foods or by natural process such as pressing, grinding or crushing. Examples such as salt, sugar, vegetable oils and fats; 3) processed foods, including products that have undergone specific preparation or preservation with the use of level 2 added to level 1 foods to preserve or to make them more palatable; 4) ultra-processed foods, including products that were made entirely or mostly from industrial formulations with artificial additives and nonculinary substances.<sup>6</sup>

We previously published the classification of food items collected with the FFQ administered in the ARIC study according to processing level.<sup>7</sup> We will classify food items collected from Carotid MRI visit following similar categorizations.

### **Diet Quality Assessment:**

Diet quality will be assessed by adherence to healthy dietary patterns (DASH, Mediterranean). For the DASH diet score, higher scores were assigned to individuals with more frequent consumption of healthy food components (fruits, vegetables, whole grains, low-fat dairy products, nuts and legumes) and lower scores were assigned to individuals with more frequent consumption of unhealthy food components (sodium, red and processed meats, sweetened beverages). Each component was scored on a scale of 1 to 5 based on ranked distribution in quintiles. The DASH diet score ranged from 8 (minimal adherence) to 40 (maximal adherence).<sup>8</sup>

For the Mediterranean diet, the score was based on higher intake of fruits, vegetables, whole grains, nuts, legumes, fish, and monounsaturated fatty acid (MUFA) to saturated fatty acid (SFA) ratio, moderate intake of alcohol, and low intake of red and processed meat. Each component was scored as 0 or 1 based on the sex-specific median intake level in the analytic sample. Participants receive 1 point for intake of each healthy food component at the median or higher, or intake of red and processed meat lower than the median. The aMED score ranged from 0 (minimal adherence) to 9 (maximal adherence).<sup>9</sup>

### **Outcomes:**

- Incident CKD was defined as reduced kidney function [estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>] and ≥25% eGFR decline, CKD-related hospitalizations or deaths, or end-stage renal disease identified through linkage with the U.S. Renal Data System registry.<sup>10</sup>
- Incident cardiovascular disease was defined as definite or probable myocardial infarction, fatal coronary heart disease, incident heart failure, or definite or probable stroke.
- All-cause mortality was defined as death from any cause using linkage to the National Death Index, telephone calls with proxies, and active surveillance of local hospital discharge records and state death records.

### **Summary of Data Analysis:**

Ultra-processed food consumption and adherence to healthy dietary patterns will be described using means, standard deviations, and percentiles, and will be visually depicted as histograms for the overall study population and stratified by age, sex, and body mass index categories. Participants will be categorized into quartiles based on scores for adherence to healthy dietary patterns and ultra-processed food consumption in late-life. We will assess the association between quartiles of ultra-processed food consumption and scores for adherence to healthy dietary patterns and demographic characteristics (sex, race), socioeconomic status (education level), health behaviors (alcohol, smoking, physical activity), and clinical factors (body mass index, blood pressure, fasting glucose, eGFR) using chi-squared tests and linear regression. Multivariable Cox proportional hazard regression models will be used to assess the association between diet quality (healthy dietary patterns, ultra-processed food) and risk of incident cardiovascular disease, incident chronic kidney disease, and all-cause mortality. Our models will account for age, sex, race, study center, body mass index, education level, smoking status, physical activity level, fasting glucose, systolic blood pressure, and estimated glomerular filtration rate (eGFR). We will also perform subgroup analysis and test for interaction by age, sex, and body mass index categories.

### **Anticipated Methodologic Limitations or Challenges:**

Ultra-processed foods intake and adherence scores of healthy dietary patterns were calculated based on self-reported dietary data, which might be prone to recall bias and social desirability bias. Survival bias could also exist as we will only include participants who have survived to attend the carotid MRI visit. Misclassification of ultra-processed foods is also possible due to the brief description of food items in the FFQ. We will follow the same rubric used in previous manuscripts on ultra-processed food and coronary artery disease and chronic kidney disease in the ARIC study, which are now published.<sup>7, 11</sup>

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript?** \_\_\_\_ Yes    ☒ No

**b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES\_OTH and/or RES\_DNA = “ARIC only” and/or “Not for Profit” ?** \_\_\_\_ Yes    \_\_\_\_ No

(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript?** \_\_\_\_ Yes    ☒ No

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES\_DNA = “No use/storage DNA”?** \_\_\_\_ Yes    \_\_\_\_ No

**9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:** <http://www.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

\_\_\_\_ ☒ Yes    \_\_\_\_ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

MP #3727 - Association between ultra-processed food consumption and risk of coronary heart disease and chronic kidney disease in the Atherosclerosis Risk in Communities Study

This previous work was conducted by Shutong Du (first author for this manuscript proposal) and Casey Rebholz (last author for this manuscript proposal), and has been published.<sup>9, 13</sup>

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?** \_\_\_\_ Yes    ☒ No

**11.b. If yes, is the proposal**

- \_\_\_ A. primarily the result of an ancillary study (list number\* \_\_\_\_\_)
- \_\_\_ B. primarily based on ARIC data with ancillary data playing a minor role  
(usually control variables; list number(s)\* \_\_\_\_\_)

\*ancillary studies are listed by number <https://sites.csc.unc.edu/aric/approved-ancillary-studies>

**12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

## References:

1. Petersen KS, Flock MR, Richter CK, Mukherjee R, Slavin JL, Kris-Etherton PM. Healthy Dietary Patterns for Preventing Cardiometabolic Disease: The Role of Plant-Based Foods and Animal Products. *Curr Dev Nutr*. 2017;1(12):cdn.117.001289. Published 2017 Nov 6. doi:10.3945/cdn.117.001289
2. Bach KE, Kelly JT, Palmer SC, Khalesi S, Strippoli GFM, Campbell KL. Healthy Dietary Patterns and Incidence of CKD: A Meta-Analysis of Cohort Studies. *Clin J Am Soc Nephrol*. 2019;14(10):1441-1449. doi:10.2215/CJN.00530119
3. Monteiro CA, Cannon G, Levy RB, et al. Ultra-processed foods: what they are and how to identify them. *Public Health Nutr*. 2019;22(5):936-941. doi:10.1017/S1368980018003762
4. Juul F, Parekh N, Martinez-Steele E, Monteiro CA, Chang VW. Ultra-processed food consumption among US adults from 2001 to 2018. *Am J Clin Nutr*. 2022;115(1):211-221. doi:10.1093/ajcn/nqab305
5. Wang L, Martínez Steele E, Du M, et al. Trends in Consumption of Ultraprocessed Foods Among US Youths Aged 2-19 Years, 1999-2018. *JAMA*. 2021;326(6):519-530. doi:10.1001/jama.2021.10238
6. Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr*. 2018;21(1):5-17. doi:10.1017/S1368980017000234
7. Du S, Kim H, Rebholz CM. Higher Ultra-Processed Food Consumption Is Associated with Increased Risk of Incident Coronary Artery Disease in the Atherosclerosis Risk in Communities Study. *J Nutr*. 2021;151(12):3746-3754. doi:10.1093/jn/nxab285
8. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women [published

correction appears in Arch Intern Med. 2008 Jun 23;168(12):1276]. *Arch Intern Med*. 2008;168(7):713-720. doi:10.1001/archinte.168.7.713\

9. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women [published correction appears in Circulation. 2009 Mar 31;119(12):e379]. *Circulation*. 2009;119(8):1093-1100. doi:10.1161/CIRCULATIONAHA.108.816736
10. Lustgarten JA, Wenk RE. Simple, rapid, kinetic method for serum creatinine measurement. *Clin Chem*. 1972;18(11):1419-1422. 30.
11. Du S, Kim H, Crews DC, White K, Rebholz CM. Association Between Ultraprocessed Food Consumption and Risk of Incident CKD: A Prospective Cohort Study [published online ahead of print, 2022 Jun 6]. *Am J Kidney Dis*. 2022;S0272-6386(22)00648-5. doi:10.1053/j.ajkd.2022.03.016