ARIC Manuscript Proposal #3727

PC Reviewed: 10/13/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association Between Ultra-processed Foods Consumption and Risk of Coronary Heart Disease and Chronic Kidney Disease in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): UPF and CHD, CKD risks

2. Writing Group:
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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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3. Timeline:
Data analysis, manuscript preparation, and writing will take place over 1.5 year.

4. Rationale:

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, accounting for more than 17 million deaths each year.[1] In the United States, CVDs remain a major cause of growing medical expenditure and health disparities. Despite great efforts have put into disease prevention and treatment over the last few decades, the prevalence of CVDs continues to grow with a projection of nearly half of the US population to have cardiovascular diseases by 2035.[2] Chronic kidney diseases (CKD) is another disease that is also prevalent in the U.S. with 15% US adults are estimated to have and the prevalence is continue increasing.[3] Many CVDs and CKD cases are attributed to common lifestyle risk factors such as level of physical activity, diet, alcohol and tobacco consumption.[4] Among these modifiable risk factors, diet is widely considered to play an influential role in preventing chronic health conditions including CVDs and CKD.

Ultra-processed foods (UPF) defined as food and drink products formulated through sequences of industrial processes, and generally contain non-culinary used substances (eg, hydrolyzed protein, modified starches, hydrogenated oils) and additives (eg. colorants, non-sugar sweeteners, emulsifiers, humectants).[5] UPF usually contain high amounts of refined carbohydrates, saturated fats, salts, added sugars, and low fiber and vitamin content.[6] Many of these nutritional features have been linked to increase risk of cardiometabolic diseases.[7] Besides their poor nutritional quality, the chemical and physical alteration they undergo, along with compounds that either generated or added during the process, are believed to pose harmful health effects.[8] However, due to the hyperpalatable, cheap and accessible nature of these type of foods, the consumption of UPF has drastically increased over the last few decades. According to nationwide cross-sectional studies, ultra-processed foods consumption contributes to as high as 60% of total energy intake in the US.[9] The rising obesity epidemic in the U.S., as well as related cardiovascular diseases and chronic kidney diseases, are correlated with a rise in ultra-processed food consumption.[10]

Previous ecological and cross-sectional evidences from Brazil, US and Europe indicated ultra-processed foods consumption is associated with excess weight gain, obesity and metabolic syndrome.[11-13] Similar results have also been published in the Seguimiento Universidad de Navarra (SUN) and NutriNet-Santé longitudinal cohorts. In addition, researchers reported an increased risk of hypertension and all-cause mortality for the highest UPF consumption group comparing the lowest consumption group in the SUN cohort.[14, 15] In the NutriNet-Santé study, consumption of UPF has also been linked to a higher risk of type 2 diabetes, all-cause mortality and incidence CVDs.[16-18] Although extensive research has been conducted in the past few years, longitudinal evidence based on US population remains scarce.[19]

In view of the current gaps, we aimed to investigate the association between ultra-processed foods consumption and the risk of CVDs and CKD in the Atherosclerosis Risk in Communities (ARIC) study, a large, prospective, observational cohort of US adults.

5. Main Hypothesis/Study Questions:

Aim 1: To evaluate the association between ultra-processed food consumption and risk of coronary heart diseases in the ARIC Study.

> **Hypothesis 1:** Higher intake of ultra-processed food is associated with higher risk of coronary heart disease (CHD).

Aim 2: To investigate how ultra-processed food consumption is associated with risk of chronic kidney disease in the ARIC Study.

> **Hypothesis 2:** Higher intake of ultra-processed food is associated with higher risk of chronic kidney disease (CKD).

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 analyze the association between ultra-processed food consumption measured at visit 1 and 3 and incident of coronary heart disease and chronic kidney disease, major risk factors of CHD and CKD (Hypertension, diabetes and obesity).

Inclusion/Exclusion:

The proposed study will include men and women with complete information on dietary intake derived from a food frequency questionnaire. We will exclude non-black and non-white participants as well as a small proportion of black participants in Minneapolis and Washington study sites. Those with 10 or more missing items on the food frequency questionnaire or derived nutrient information at visit 1, missing covariates (age, gender, race, BMI, leisure time activities, smoking and drinking status, education level, diabetes and hypertension status, eGFR levels), or implausibly low caloric intake or high caloric intake will be excluded (women: <500 or >3500 kcal; men: <600 or >4500 kcal). Participants with prevalent CHD and CKD diseases at baseline will be excluded as well.

Dietary Assessment:

A 66-item semi-quantitative food frequency questionnaire (modified version of the Willett/Harvard food frequency questionnaire[20, 21)] was used to collect participants' usual intake of foods and beverages in the past year by trained interviewers at visit 1 and 3. Different sizes of cups and glasses were referenced to illustrate portion sizes. We incorporated both visit 1 and 3 food frequency questionnaire data and calculated the cumulative average in order to improve the estimation of usual dietary intakes[22].

Definition of Ultra-processed foods:

We will use the NOVA classification system to categorize each reported food items on the food frequency questionnaire into one of the following groups: (Group 1) Unprocessed or minimally processed foods (Obtained directly from plants or animals, undergo little or no alteration following their removal from nature); (Group 2) Processed culinary ingredients (Extracted from natural foods or from nature by processes such as pressing, grinding, crushing, pulverizing, and refining); (Group 3) Processed foods (Products manufactured by industry with the use of group 2 added to group 1 to preserve or to make them more palatable); (Group 4) Ultra-processed foods (Industrial formulations made entirely or mostly from substances extracted from foods)[23].

Outcome Ascertainment:

Incident CHD will be defined as hospitalized Myocardial Infarction or fatal CHD. ARIC staff identified incident CHD through active surveillance on cardiovascular disease-related hospitalizations and deaths, and cases were adjudicated by a group of experts.

Incident CKD will be defined as either a decrease in kidney function (glomerular filtration rate eGFR <60 ml/min/1.73 m2) or presence of kidney damage (usually represented by urinary albumin excretion ⩾30 mg/day).[24] Serum creatinine was collected at visit 1, visit 2, visit 4, and visit 5 using the modified kinetic Jaffe method. Estimated glomerular filtration rate (eGFR) based on serum creatinine and cystatin will be calculated by the 2009 Chronic Kidney Disease Epidemiology Collaboration equation.[25]

Statistical analyses:

We will calculate the cumulative average consumption (servings/day) of each food item in the food frequency questionnaire for each person using both visit 1 and 3 data and assign the level of intake for each food item into 4 groups according to the NOVA classification. We will then calculate the energy-adjusted consumption of the ultra-processed foods (group 4) and assign participants into 4 quartiles based on their energy-adjusted consumption of the ultra-processed food.

We will examine participants baseline characteristics and nutritional characteristics according to the quartiles of energy adjusted ultra-processed food consumption. To test the difference by quartiles, we will use chi-square tests for categorical variable and weighted ANOVA for continuous variable.

We will perform Cox proportional hazards models, with years of follow-up as the time matric, to calculate hazard ratios (HR) and 95% CI for the association between frequency of ultra-processed food intake and incident CHD and CKD events. Model 1 will adjust for age, sex, race, study sites and total energy intake. Model 2 will further adjust for smoking and drinking status, physical activity during leisure time and education levels. In Model 3, we will add baseline BMI, hypertension and diabetes status and eGFR levels into our previous model to test the mediating effect because these factors may be along the causal pathway. linear trend will be tested across quartiles using the median value within each quartile. In addition to that, we will perform subgroup analyses to identify potential effect modifiers and test for interaction terms. Finally, we will use cubic spline regression to test for nonlinearity between UPF servings per day and the risk of CHD and CKD.

Limitations and challenges:

Misclassifications in the NOVA categories is possible and there are many food items in the diet that the food frequency questionnaire may not account for.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x__ 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 __x__ 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.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___x___ 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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ 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.cscc.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.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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