ARIC Manuscript Proposal #4006

PC Reviewed: 2/8/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Ultra-Processed Food Consumption and Risk of Hypertension in US Adults

b. Abbreviated Title (Length 26 characters): UPF and Hypertension

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

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3. Timeline: Data analysis, and manuscript writing will take place over one year. This project will be completed as Mr. Rivera's thesis project, with an ultimate deadline of graduation (May 2023).

4. Rationale:

Ultra-processed foods are industrially manufactured, ready-to-eat/heat formulations that contain additives and are mostly lacking in whole foods.[1] These foods are nutritionally poor, are typically high in sugar, refined carbohydrates, and salt, and low in fiber and micronutrients. The consumption of ultra-processed food in the U.S. is high. One study found that from 2011 to 2016, UPFs constituted over half of the total energy intake of the average US citizen.[2] These foods are easily accessible and becoming more common in the food supply.[3] It has been reported recently that the consumption of ultra-processed food in the U.S. is increasing over the past two decades in children and adults.[2,4]

There is a growing body of literature demonstrating that the consumption of ultra-processed food is associated with a wide range of adverse cardiometabolic health consequences.[5] It has been proposed that ultra-processed foods have been influential in contributing to the burden of chronic diseases. Studies on this topic have predominantly been derived from non-U.S. study populations. For example, studies conducted in Brazil, Spain, and Canada indicate that higher consumption of ultra-processed food is associated with higher risk of incident hypertension.[6-9] These findings were consistent across studies populations with an estimated 30% higher risk of incident hypertension in the highest versus lowest category of intake after accounting for confounding factors. There is limited evidence on the health consequences of ultra-processed food consumption, and the impact on hypertension risk specifically, conducted in U.S. study populations.

Our study differentiates itself from previous ones for several reasons. First, the aforementioned studies were conducted on populations much less racially heterogeneous than the United States. This gives our study and its results more generalizability to a broader population. Second, the data we are analyzing comes from the ARIC study. The data has high validity, comes from diverse populations, and the data spans decades of life.

5. Main Hypothesis/Study Questions:

Specific Aim: To assess the prospective association between consumption of ultra-processed food and incident hypertension over long-term follow-up in black and white adults in the US.

> *Hypothesis*: We hypothesize that higher intake of ultra-processed food will be associated with a higher risk of hypertension.

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 conduct a prospective analysis with visit 1 as baseline, and participants will be followed for the development of hypertension.

Inclusion/Exclusion: We will exclude on the basis of the following criteria:

1) Missing or implausible dietary data
    a. Missing derived nutritional data (total energy intake)
    b. <500 or >3500 kcal/day for women, <600 or >4500 kcal for men
    c. Missing 10 or more items on the food frequency questionnaire
2) Missing covariates [age, sex, race, center, education level as a proxy for socioeconomic status, smoking status, physical activity level, fasting glucose, and estimated glomerular filtration rate (eGFR)]
3) Prevalent hypertension
4) Non-black and non-white participants, black participants from Minneapolis, Minnesota, and black participants from Washington County, Maryland

Dietary Assessment:

Dietary intake was assessed in the ARIC study using a semi-quantitative 66-item food frequency questionnaire (FFQ) which was modified from the original Willett FFQ. [10,11] Participants reported their usual intake of food items of a specified portion size during the preceding year. The FFQ was administered at baseline (study visit 1) and study visit 3 by trained interviewers. To improve precision of estimates of dietary data, we will incorporate data collected at both time points using the cumulative average. Visit 1 dietary data will be used for those who developed hypertension or were censored between visits 1 and 3. Otherwise, we will use the average of dietary data from visits 1 and 3 for those who were followed for the development of incident hypertension after visit 3. Nutrient intake was derived by multiplying the daily servings of each food item by its nutrient content which was obtained primarily from U.S. Department of Agriculture sources.

Classification of Ultra-Processed Food (Exposure):

All food items on the FFQ were classified into one of four categories according to the NOVA classification system based on processing level: 1) unprocessed or minimally processed foods, including foods that are fresh or slightly modified by methods such as freezing, drying or pasteurization, with no addition of culinary ingredients; 2) processed culinary ingredients, including substances extracted from natural foods or by natural process and were used in culinary preparations, such as salt, sugar, vegetable oils and fats; 3) processed foods, including products that have undergone specific preparation or preservation with the use of culinary ingredients to make it last longer or taste better; and 4) ultra-processed foods, including products that were made entirely or mostly from industrial formulations with artificial additives such as sweeteners and preservatives.[12] We previously published the classification of food items on the ARIC study FFQ according to processing level.[13] For food items that were indistinct with their processing level (e.g., fruit juices, yogurt), we made educated assumptions based on past literature and nutritional characteristics of these food items.[14,15] Within each NOVA category, we calculated the total daily consumption for each participant (servings per day), adjusted for energy using the residual method, and then assigned participants to quartiles based on the ranked distribution of energy-adjusted frequency of consumption of ultra-processed food.[16]

Ascertainment of Incident Hypertension (Outcome):

Blood pressure was measured multiple times at each study visit by certified technicians using a random zero sphygmomanometer after the participants rested for 5 minutes in a seated position. Participants self-reported physician diagnosis of hypertension and all medications were transcribed. Annual follow-up phone interviews have been conducted since study visit 4 to collect information about participants' health status, including hypertension diagnosis and anti-hypertensive medication use. Incident hypertension is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, hypertension diagnosis, or use of anti-hypertensive medication.[17] Similar definitions of incident hypertension have been used in the ARIC study.[18-20] Alternative definitions will be investigated in sensitivity analyses, e.g. using elevated blood pressure only and using more contemporary definitions of hypertension (lower blood pressure thresholds).[21] Active surveillance was used to ascertain vital status through linkage to the National Death Index, hospital discharge records, obituaries, and phone calls with proxies. Vital status will be used to censor participants in survival analysis of incident hypertension.

Analytic Strategy:

Survival analysis, including Kaplan-Meier and Cox proportional hazards regression models, will be used to evaluate the prospective association between ultra-processed food at visit 1 and risk of hypertension during approximately 30 years of follow-up with censoring for death and end of follow-up. In addition, we will use linear mixed models in order to incorporate repeated measures of blood pressure across follow-up study visits and account for the non-independence of the repeated measures within individuals using random effects. β coefficients (for the analysis of blood pressure) and hazard ratios (for the analysis of incident hypertension) will be calculated according to quartiles of ultra-processed food with quartile 1 as the reference group. We will also explore non-linear associations between ultra-processed food and blood pressure/hypertension status using cubic and linear splines. We will perform a secondary analysis of ultra-processed food items. We will use multivariable regression models to examine the independent association between ultra-processed food and blood pressure/hypertension after accounting for known risk factors, including age, sex, race, center, education level as a proxy for socioeconomic status, smoking status, physical activity level, fasting glucose, and estimated glomerular filtration rate (eGFR). We will test for interaction by sex and race using likelihood ratio tests and, if present, stratify the analysis by these factors.

Methodological limitations or challenges:

1) The precise time of development of hypertension is not observed. Therefore, we will explore regression techniques that fit interval-censored survival data (i.e., Weibull regression using the **stintreg** command in Stata).
2) Exposure misclassification of food into processing level categories using the NOVA classification system is possible. The relatively short length of the questionnaire could result in an underestimation of the absolute intake of ultra-processed food. However, we should be able to adequately rank participants within the population according to consumption of ultra-processed food. There is relatively less detailed information available about specific foods in the ARIC study compared to dietary data collected using other assessment tools (e.g., 24-hour dietary recall). We will use the rubric used in a previous manuscript on ultra-processed food and coronary heart disease in the ARIC study, which has passed peer review and is now published.

3) The FFQ, like most questionnaires, is subject to measurement error and recall bias.
4) Observational studies are subject to confounding due to imprecisely measured or unmeasured covariates.

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/aricproposals/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)?

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

The present proposal assesses an outcome (incident hypertension) which was not analyzed as part of the previous proposal (coronary heart disease, chronic kidney disease). All authors on the previous proposal are invited to join the present proposal.

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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