ARIC Manuscript Proposal #4308

PC Reviewed: 8/8/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Ultra-processed food consumption and risk of incident diabetes in the ARIC study

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

2. Writing Group:

Writing group members:

- Shutong Du
- Valerie Sullivan
- Michael Fang
- Liz Selvin
- 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]**

First author: Shutong Du
Address: Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St
Baltimore MD 21205

Phone: 206-601-3274 Fax:
E-mail: sdu12@jhu.edu

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).
Name: Casey M. Rebholz
Address: 2024 E. Monument St, Suite 2-500
Baltimore MD 21287

Phone: 410-502-2359 Fax:
E-mail: crebhol1@jhu.edu

3. Timeline:

Data analysis and manuscript preparation is anticipated to take place within one year of approval of this proposal.

4. Rationale:

Ultra-processed foods are defined as industrial food formulations that have undergone multiple processing steps, with the addition of non-culinary and chemical substances to enhance appearance, flavor, and shelf life. These foods are often high in sugar, salt, and fat, and low in protein, fiber, and micronutrients. Previous evidence has suggested that higher consumption of ultra-processed foods is associated with adverse health outcomes, including metabolic syndrome, obesity, cardiovascular disease, chronic kidney disease, cancers, and mortality (1-6).

Since obesity is a well-established risk factor for type 2 diabetes, and ultra-processed food consumption has been linked to weight gain and obesity, it is crucial to determine whether ultra-processed foods is related to diabetes risk independent of body mass status or is mediated by weight gain. Teasing apart this relationship can guide targeted interventions and management strategies.

Most of the previous studies on ultra-processed food and their health impacts were conducted in European populations, which have different consumption levels and food preferences compared to the U.S. population (7, 8). Studies conducted in the U.S. have consisted of predominantly white populations (9). Given that diabetes disproportionally affects non-white individuals in the U.S., it is important to examine the association between ultra-processed food consumption and diabetes risk within a diverse population, to allow for broader generalizability.

Diet is a modifiable risk factor for diabetes. Assessing change in diet, particularly regarding ultra-processed food consumption, is essential for developing prevention strategies that can alleviate the public health burden of diabetes.

Given the increasing consumption of ultra-processed foods (10), our study aims to: 1) investigate the relationship between ultra-processed food consumption and diabetes risk and explore the role of body mass index in the association between ultra-processed foods and diabetes; and 2) evaluate changes in ultra-processed food intake over a 6-year period and its impact on subsequent diabetes risk. This comprehensive approach will provide valuable insights into the complex interplay between diet, obesity, and diabetes, helping inform targeted interventions for diabetes prevention and management.

5. Main Hypothesis/Study Questions:

Specific Aim 1: To evaluate the association between ultra-processed food consumption and risk of incident diabetes.

> **Hypothesis 1:** Higher ultra-processed food consumption is associated with a higher risk of incident diabetes.

Specific Aim 2: To evaluate the association between change in ultra-processed food intake and risk of incident diabetes.

Hypothesis 2: An increase over time in consumption of ultra-processed food or sustained high level of intake of ultra-processed food during a 6-year period is associated with a higher risk of incident diabetes.

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 first investigate the association between ultra-processed foods consumption assessed at visit 1 and subsequent risk of incident diabetes during follow-up. Then, we will calculate the change in ultra-processed foods intake between visit 1 and visit 3 and risk of incident diabetes after visit 3.

Inclusion/Exclusion Criteria:

We will exclude participants based on the following criteria:

1. Participants with missing dietary intake information or derived nutrient information (missing more than 10 items).
2. Participants with missing or implausible energy intake data (women: <500 or >3500 kcal; men: <600 or >4500 kcal).
3. Non-black and non-white participants.
4. Black participants in Minneapolis, Minnesota and Washington County, Maryland study sites.
5. Participants with missing covariates (age, gender, race-center, body mass index, leisure time physical activity, smoking status, education level, total cholesterol, systolic blood pressure, and fasting glucose).
6. Participants with prevalent diabetes at baseline defined as elevated glucose levels (defined as a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL), self-reported diagnosis, or medication use.

Dietary Assessment:

A 66-item semi-quantitative food frequency questionnaire (FFQ) that was modified from the Willett food frequency questionnaire was used to collect information on consumption of foods and beverages in the past year. The questionnaire was administered by trained interviewers at study visits 1 and 3, and different sizes of cups and glasses were provided to the participants to help visualize the portion size. Food questionnaire answers ranged from almost never to more than 6 times per day.

Classification of Ultra-Processed Food and Assessment of Diet Changes:

We used the NOVA classification system to categorize 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 (e.g., drying, boiling, pasteurizing, squeezing) or no alteration following their removal from nature.

- Group 2 (processed culinary ingredients): Extracted from natural foods or from nature through processes such as pressing, grinding, crushing, pulverizing, and refining. These ingredients are mainly used to prepare, season, or cook the foods from Group 1.
- Group 3 (processed foods): A combination of foods from Group 1 and Group 2, used for preservation or to enhance taste.
- Group 4 (ultra-processed foods): Industrial formulations made entirely or mostly from substances extracted from foods, with little or no intact foods. These foods often contain non-culinary substances (e.g., colorants, emulsifiers, and sweeteners).

We have applied this classification system in previous published papers on ultra-processed food in the ARIC study (3, 4).

We will categorize ultra-processed food intake at visit 1 as low (below or equal to median) or high (higher than the median), then categorize changes between visit 1 and 3 as sustained low (low in both visits), sustained high (high in both visits), increased intake (low at visit 1, high at visit 3), or decreased intake (high at visit 1, low at visit 3).

Outcome assessment:

Incident diabetes will be defined by the following three criteria used in prior ARIC study publications (11, 12, 13):

- Elevated blood glucose levels (a fasting glucose $\geq$ 126 mg/dL or a non-fasting glucose $\geq$ 200 mg/dL), or $HbA_{1C} \geq 6.5\%$ (when available).
- Current use of diabetes medication.
- Self-report of a physician diagnosis of diabetes.

As a sensitivity analysis, we will define incident diabetes based on treated diabetes (medication use) only.

Statistical Analysis:

We will summarize participants' baseline characteristics and nutritional characteristics according to the quartiles of energy-adjusted ultra-processed food consumption. We will use chi-square tests for categorical variables and ANOVA for continuous variable to test for differences in participant characteristics and nutritional factors between quartiles of ultra-processed food intake.

We will use Cox proportional hazards models, with time on study as the time metric, to calculate hazard ratios (HR) and 95% CI for the association between baseline ultra-processed food consumption and risk of diabetes using quartile 1 as the reference group. We will use Cox proportional hazards models to assess change in ultra-processed foods intake and time to incident diabetes since visit 3. Model 1 will adjust for age, sex, race, study center, and total energy intake. Model 2 (main model) will further adjust for drinking status, leisure time physical activity, and education level. In Model 3, we will further adjust for total cholesterol, systolic blood pressure, and fasting glucose. In Model 4, we will additionally adjust for body mass index. We will test for linear trend across quartiles using the median intake within each quartile. We will also perform subgroup analyses (sex, race, body mass index categories) to identify potential effect modifiers and test for interaction terms using likelihood ratio tests. We will also model ultra-processed food intake as a continuous variable (servings/day) and assess the risk of diabetes associated with each additional serving consumed per day. We will also model ultra-processed food intake using restricted cubic splines to visually examine and test for linearity of the association.

We will assess the associations between specific ultra-processed food subgroups (e.g., sugar-sweetened beverages, breakfast cereals, ultra-processed meats, dairy products) and risk of diabetes to identify food groups that contribute to the overall association between ultra-processed food and diabetes. We will also perform mediation analysis to estimate the percentage of the associations between ultra-processed food intake and diabetes risk mediated by body mass index.

Anticipated Methodologic Limitations or Challenges:

Our dietary intake data were self-reported, which may be prone to measurement error and recall bias. The food descriptions provided by the FFQ might not offer sufficient information to accurately classify food processing levels, leading to potential misclassification error. We will classify uncertain food items conservatively, meaning we will classify them in a less processed categories when in doubt. We have previously used this classification system to characterize processing level of foods consumption in the ARIC study and we observed that higher intake of ultra-processed food is associated with elevated risk of incident chronic kidney disease and incident coronary heart disease (3, 4). Additionally, the dietary intake data collected in the late 1980s may not accurately reflect the current consumption of ultra-processed foods. However, the timing of the dietary data collection allows for long-term observation of the development of diabetes.

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.cscc.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 (3, 4).

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.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.

References:

1. Canhada SL, Vigo Á, Luft VC, et al. Ultra-Processed Food Consumption and Increased Risk of Metabolic Syndrome in Adults: The ELSA-Brasil. Diabetes Care. 2023;46(2):369-376. doi:10.2337/dc22-1505
2. Valicente VM, Peng CH, Pacheco KN, et al. Ultraprocessed Foods and Obesity Risk: A Critical Review of Reported Mechanisms. Adv Nutr. 2023;14(4):718-738. doi:10.1016/j.advnut.2023.04.006
3. 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
4. Du S, Kim H, Crews DC, White K, Rebholz CM. Association Between Ultraprocessed Food Consumption and Risk of Incident CKD: A Prospective Cohort Study. Am J Kidney Dis. 2022;80(5):589-598.e1. doi:10.1053/j.ajkd.2022.03.016
5. Isaksen IM, Dankel SN. Ultra-processed food consumption and cancer risk: A systematic review and meta-analysis. Clin Nutr. 2023;42(6):919-928. doi:10.1016/j.clnu.2023.03.018
6. Suksatan W, Moradi S, Naeini F, et al. Ultra-Processed Food Consumption and Adult Mortality Risk: A Systematic Review and Dose-Response Meta-Analysis of 207,291 Participants. Nutrients. 2021;14(1):174. Published 2021 Dec 30. doi:10.3390/nu14010174
7. Levy RB, Rauber F, Chang K, et al. Ultra-processed food consumption and type 2 diabetes incidence: A prospective cohort study. Clin Nutr. 2021;40(5):3608-3614. doi:10.1016/j.clnu.2020.12.018
8. Llavero-Valero M, Escalada-San Martín J, Martínez-González MA, Basterra-Gortari FJ, de la Fuente-Arrillaga C, Bes-Rastrollo M. Ultra-processed foods and type-2 diabetes risk in the SUN project: A prospective cohort study. Clin Nutr. 2021;40(5):2817-2824. doi:10.1016/j.clnu.2021.03.039
9. Chen Z, Khandpur N, Desjardins C, et al. Ultra-Processed Food Consumption and Risk of Type 2 Diabetes: Three Large Prospective U.S. Cohort Studies. Diabetes Care. 2023;46(7):1335-1344. doi:10.2337/dc22-1993
10. 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
11. Xu Z, Steffen LM, Selvin E, Rebholz CM. Diet quality, change in diet quality and risk of incident CVD and diabetes. Public Health Nutr. 2020;23(2):329-338. doi:10.1017/S136898001900212X
12. He X, Rebholz CM, Daya N, Lazo M, Selvin E. Alcohol consumption and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2019;62(5):770-778. doi:10.1007/s00125-019-4833-1
13. Rooney MR, Rawlings AM, Pankow JS, et al. Risk of Progression to Diabetes Among Older Adults With Prediabetes [published correction appears in JAMA Intern Med. 2021 Apr 1;181(4):570]. JAMA Intern Med. 2021;181(4):511-519. doi:10.1001/jamainternmed.2020.8774