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Higher Ultra-Processed Food Consumption Is Associated with Increased Risk of Incident Coronary Artery Disease in the Atherosclerosis Risk in Communities Study

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ABSTRACT

Background: Higher ultra-processed food intake has been linked with several cardiometabolic and cardiovascular diseases. However, prospective evidence from US populations remains scarce.

Objectives: To test the hypothesis that higher intake of ultra-processed foods is associated with higher risk of coronary artery disease.

Methods: A total of 13,548 adults aged 45–65 y from the Atherosclerosis Risk in Communities study were included in the analytic sample. Dietary intake data were collected through a 66-item FFQ. Ultra-processed foods were defined using the NOVA classification, and the level of intake (servings/d) was calculated for each participant and divided into quartiles. We used Cox proportional hazards models and restricted cubic splines to assess the association between quartiles of ultra-processed food intake and incident coronary artery disease.

Results: There were 2006 incident coronary artery disease cases documented over a median follow-up of 27 y. Incidence rates were higher in the highest quartile of ultra-processed food intake (70.8 per 10,000 person-y; 95% CI: 65.1, 77.1) compared with the lowest quartile (59.3 per 10,000 person-y; 95% CI: 54.1, 65.0). Participants in the highest compared with lowest quartile of ultra-processed food intake had a 19% higher risk of coronary artery disease (HR: 1.19; 95% CI: 1.05, 1.35) after adjusting for sociodemographic factors and health behaviors. An approximately linear relation was observed between ultra-processed food intake and risk of coronary artery disease.

Conclusions: Higher ultra-processed food intake was associated with a higher risk of coronary artery disease among middle-aged US adults. Further prospective studies are needed to confirm these findings and to investigate the mechanisms by which ultra-processed foods may affect health. *J Nutr* 2021;151:3746–3754.

Keywords: ultra-processed foods, coronary artery disease, cardiovascular disease, ARIC, NOVA classification, diet and nutrition, epidemiology

Introduction

Cardiovascular disease is the leading cause of death worldwide, accounting for more than 17 million deaths each year (1). In the United States, cardiovascular disease remains a major cause of growing medical expenditures and health disparities. Despite prevention and treatment efforts over the last few decades, the prevalence of cardiovascular disease continues to grow, with a projection of nearly half of the US population developing cardiovascular disease by 2035 (2). A large proportion of cardiovascular disease cases are attributed to modifiable lifestyle risk factors, including diet (3).

Ultra-processed foods are defined as food and drink products formulated through industrial processes, and they generally contain nonculinary substances (e.g., hydrolyzed protein, modified starches, hydrogenated oils) and additives (e.g., colorants, nonsugar sweeteners, emulsifiers, humectants). Ultra-processed foods usually contain high amounts of refined carbohydrates, saturated fat, salt, and sugar, and are low in fiber and vitamins (4). Many of these nutritional factors have been linked to increased risk of cardiometabolic diseases (5). In addition to the poor nutritional quality of ultra-processed foods, the chemical and physical alterations they undergo, along with compounds that are either generated or added during the process, are believed to pose negative health effects (6). However, due to their hyperpalatable, inexpensive, and accessible nature, the consumption of ultra-processed foods has drastically increased over the last few decades. According to a nationwide cross-sectional study (NHANES), ultra-processed food consumption contributes to as high as 60% of total energy intake in the

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United States (7). The rising obesity epidemic in the United States, as well as related cardiovascular diseases, are correlated with a rise in ultra-processed food consumption (8).

Previous ecological and cross-sectional evidence from Brazil, Europe, and the United States indicated that ultra-processed food consumption is associated with excess weight gain, obesity, and metabolic syndrome (9–11). Longitudinal studies have provided evidence of a temporal relation between ultra-processed food intake and adverse cardiometabolic outcomes. Investigators have reported higher risk of incident hypertension, obesity, and all-cause mortality for those with a higher intake of ultra-processed food consumption group in the Seguimiento Universidad de Navarra cohort study conducted in Spain (12–14). In the NutriNet-Santé study conducted in France, consumption of ultra-processed foods was prospectively linked to a higher risk of type 2 diabetes, incident cardiovascular disease, and all-cause mortality (15–17). Even though the United States has one of the highest volumes of sales of ultra-processed foods per capita in the world (18), there is limited research on the prospective association between ultra-processed food consumption and cardiovascular disease risk in US populations.

In light of the current gaps in the literature, we aimed to investigate the prospective association between ultra-processed food consumption and the risk of incident coronary artery disease (CAD) in the Atherosclerosis Risk in Communities (ARIC) study, a large cohort of US adults.

Methods

Study population

The ARIC study is a community-based prospective cohort study of cardiovascular disease and its risk factors conducted in middle-aged US adults, predominately black and white men and women (19). The baseline population included 15,792 participants aged 45–64 y recruited in 1987–1989 from 4 communities in the United States: Washington County, MD; suburbs of Minneapolis, MN; Forsyth County, NC; and Jackson, MS. There have been 6 follow-up study visits, conducted in 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), 2011–2013 (visit 5), 2016–2017 (visit 6), and 2018–2019 (visit 7). The institutional review board at each site approved the study protocol, and all participants provided informed consent at each study visit. Procedures were followed in accordance with the ethical standards of the institutional review boards.

Our analytic sample included adults with ≤10 missing items on the FFQ and no missing data for baseline covariates (n = 14,976) (**Supplemental Figure 1**). Participants were excluded if they reported implausibly low or high energy intake (<600 or >4500 kcal/d for men and <500 or >3500 kcal/d for women, n = 6); had a history of CAD (n = 1332), were neither white nor black, or were black individuals from Washington County and suburbs of Minneapolis (n = 90), who were excluded due to small numbers. Our final sample size was 13,548.

Dietary assessment and ultra-processed food classification

Usual food intake was assessed by trained interviewers at baseline (1987–1989) and visit 3 (1993–1995) using a 66-item semiquantitative FFQ, modified from the Willett FFQ (20, 21). Different sizes of measuring cups and glasses were referenced to illustrate portion sizes. Participants reported how often on average they consumed each food item of a particular portion size in the previous year. Nutrient intake was calculated by multiplying self-reported frequency of consumption and portion size by the nutritional content of each food item from USDA data sources.

We used the NOVA classification system to categorize each reported food item in the FFQ into 1 of the following groups based on levels of processing: *1*) unprocessed or minimally processed foods (obtained directly from plants or animals, with little or no alteration); *2*) processed culinary ingredients (extracted from natural foods or from nature and has undergone processes such as pressing, grinding, crushing, pulverizing, and refining); *3*) processed foods (products manufactured by industry with the use of group 2 added to group 1 to preserve or to make them more durable); *4*) ultra-processed foods (industrial formulations made entirely or mostly from substances extracted from foods) (22). Examples of foods in all of these 4 categories are presented in **Supplemental Table 1**.

We focused on the ultra-processed food group for the present study. We incorporated dietary intake data from both visit 1 and visit 3 to improve the estimation of usual dietary intake (23). Specifically, visit 1 dietary intake data were used for those who developed CAD or were censored between visit 1 and visit 3. The average of visit 1 and visit 3 values was used for those who developed CAD or were censored after visit 3. We then adjusted for total energy intake using the residual method (24) and divided participants into quartiles based on their intake of ultra-processed food consumption at baseline (25).

Outcome ascertainment

CAD events were ascertained by a variety of techniques, including annual telephone interviews, to obtain information on hospitalizations and health events that occurred during the prior year. Additional cardiovascular events were detected by active surveillance of discharge lists from local hospitals and linkage to the National Death Index (19, 26). Trained medical chart abstractors recorded chest pain, cardiac enzyme concentrations, and up to three 12-lead electrocardiograms (ECGs) for hospitalized individuals. The ECGs were coded using the Minnesota Code and waveform changes were evaluated by trained technicians (27). Death certificates, interviews with ≥1 next of kin, and questionnaires completed by patients' physicians were used for out-of-hospital death investigation. Coroner reports and autopsy reports were obtained for validation when available.

CAD incidence was defined as the first occurrence of a definite or probable hospitalization due to myocardial infarction (MI) or definite CAD death (26). Definite or probable MI hospitalization was identified by chest pain, cardiac enzyme concentrations, and/or ECG readings. Definite CAD death was defined based on a combination of chest pain symptoms, medical history, and relevant ICD-9 codes (410–414, 427.5, 429.2 and/or 799) from the death certificate. The ARIC Morbidity and Mortality Classification Committee reviewed and validated all potential clinical CAD diagnoses using published criteria and decided upon the final classification (26).

Measurement of covariates

Participants reported sociodemographic characteristics (age, race, sex, education level), health behaviors (smoking status, drinking status, physical activity), and medical history (diagnosed disease) through a validated questionnaire administered by trained interviewers. BMI (in kg/m^2) was calculated from measurements of weight to the nearest pound and height to the nearest centimeter, with the participants wearing a scrub suit and no shoes. Blood creatinine was measured

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Supplementary Figures 1 and 2 and Supplementary Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn.
Address correspondence to CMR (e-mail: crebhol1@jhu.edu).
Abbreviations used: ARIC, Atherosclerosis Risk in Communities; CAD, coronary artery disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; IU, international unit; MI, myocardial infarction.

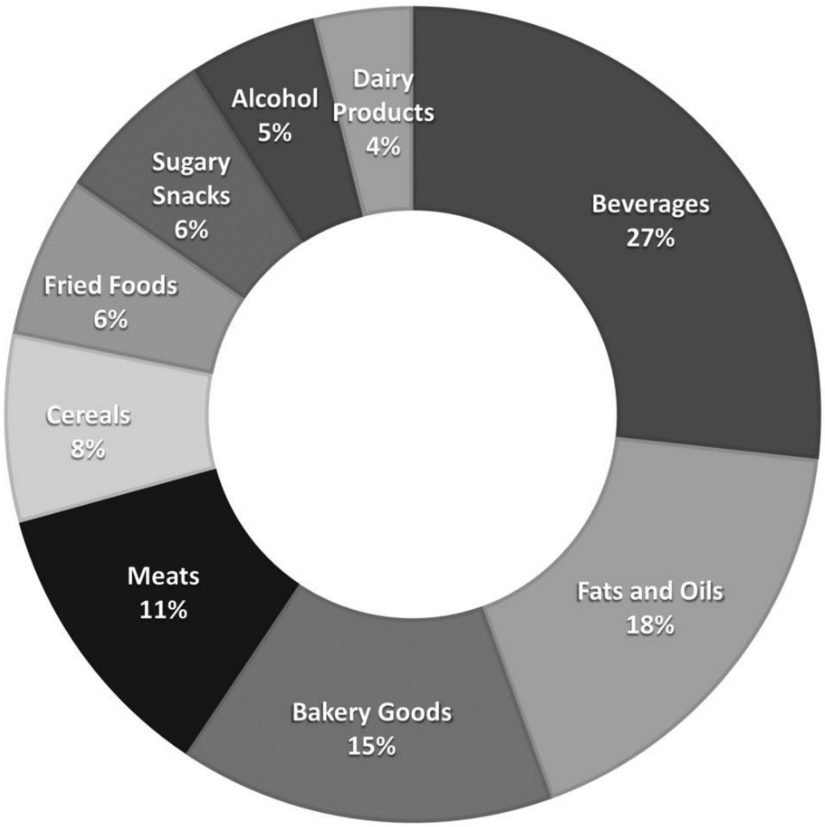

FIGURE 1 Proportion (%) of each food group contributing to the frequency (servings/d) of ultra-processed food consumption in the Atherosclerosis Risk in Communities Study. Dairy products: ice cream; fats and oils: margarine; meats: hamburgers, hot dogs, processed meats (sausage, salami, bologna), beef, pork, or lamb in dishes; sugary products: chocolate bars or pieces (Hershey's, plain M&M's, Snickers, Reese's), candy without chocolate; bakery goods: ready-made pie, donuts, biscuits, or cornbread; Danish pastry, sweet roll, coffee cake, croissant, cookies, cake, or brownie; cereals: cold breakfast cereal; fried foods: potato chips or corn chips, French fried potatoes, food fried away from home; beverages: orange or grapefruit juice, low calorie and regular soft drinks, fruit-flavored punch or noncarbonated beverages (lemonade, Kool-Aid, Hawaiian Punch); liquor: hard liquor.

using the modified kinetic Jaffé method, standardized according to the National Institute of Standards and Technology standard, with calibrations accounting for between-assay variation (28, 29). Serum total cholesterol concentration was assessed using the enzymatic method from a single aqueous reagent (30).

Participants were classified as normal weight (BMI <25), overweight (BMI ≥25 or <30 kg/m^2), or obese (BMI ≥30). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication in the preceding 2 wk. Diabetes was defined as fasting blood glucose concentration ≥126 mg/dL, nonfasting blood glucose concentration ≥200 mg/dL, self-reported history of diagnosed diabetes, or use of current diabetes medication in the preceding 2 wk. Kidney function was described by stages of chronic kidney disease using estimated glomerular filtration rate (eGFR), which was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using blood creatinine (31).

Statistical analyses

Baseline characteristics and nutritional characteristics were examined according to quartiles of frequency of ultra-processed food consumption, using means ± SDs for continuous variables, and proportions for categorical variables.

We used multivariable Cox proportional hazards models, with years of follow-up from the baseline as the time metric, to calculate HRs and 95% CIs for the association between quartiles of ultra-processed food intake and incident CAD. We used the median value of each quartile to test for linear trends across quartiles. Model 1 adjusted for demographic characteristics (age, sex, total energy intake, and a combined term for race and study center). We used a combined term for race and study center to account for nonuniform racial distribution of participants in each study center. Model 2 additionally adjusted for socioeconomic level (education level) and health behaviors (smoking and drinking status, physical activity during leisure time). We considered model 2 as the main model.

We performed a mediation analysis to examine potential mediators (BMI, total serum cholesterol concentration, eGFR, hypertension status, and diabetes status) along the causal pathway between ultra-processed foods and incident CAD (**Supplemental Figure 2**).

In model 2, we conducted subgroup analyses by sex, race, BMI categories, diabetes status, and hypertension status. We performed likelihood ratio tests with interactions terms to test whether the association between ultra-processed foods and incident CAD differed across subgroups.

We used a restricted cubic spline with 4 knots at the 5th, 35th, 65th, and 95th percentiles to visually depict the shape of the association between ultra-processed food consumption and CAD risk in our multivariable Cox proportional models. The reference level was set at the 25th percentile of ultra-processed food consumption (4.02 servings/d). We also explored the association between each additional serving of ultra-processed foods above the reference level and the risk of incident CAD during follow-up.

Sensitivity analyses were performed by excluding the first 2 y of follow-up for all participants to minimize the possibility of competing risk due to other underlying health conditions at baseline. Additionally, we excluded the first 5 y of follow-up and CAD cases that were diagnosed within that period to avoid potential reverse causation. All data analyses were performed using Stata version 16.0 (StataCorp, LLC).

TABLE 1 Baseline characteristics according to quartiles of ultra-processed food consumption in the Atherosclerosis Risk in Communities Study[1]

	Quartile 1 ($n = 3343$)	Quartile 2 ($n = 3395$)	Quartile 3 ($n = 3430$)	Quartile 4 ($n = 3380$)
Ultra-processed food intake, servings/d	3.9 ± 0.9	5.4 ± 0.3	6.4 ± 0.3	8.4 ± 1.6
Age, y	54.2 ± 5.8	54.1 ± 5.8	54.0 ± 5.7	53.7 ± 5.7
Female	1908 (57.1%)	1970 (58.0%)	1940 (56.6%)	1750 (51.8%)
Black	966 (28.9%)	1042 (30.7%)	910 (26.5%)	574 (17.0%)
Study center				
Minneapolis, MN	758 (22.7%)	758 (22.3%)	870 (25.4%)	1197 (35.4%)
Jackson, MS	844 (25.2%)	952 (28.0%)	829 (24.2%)	491 (14.5%)
Washington County, MD	781 (23.4%)	799 (23.5%)	844 (24.6%)	937 (27.7%)
Forsyth County, NC	960 (28.7%)	886 (26.1%)	887 (25.9%)	755 (22.3%)
Education level				
Less than high school	724 (21.7%)	767 (22.6%)	797 (23.2%)	703 (20.8%)
High school	968 (29.0%)	1109 (32.7%)	1163 (33.9%)	1173 (34.7%)
Higher than high school	1651 (49.4%)	1519 (44.7%)	1470 (42.9%)	1504 (44.5%)
BMI				
Normal weight, <25.0	1217 (36.4%)	1173 (34.6%)	1175 (34.3%)	1043 (30.9%)
Overweight, 25.0 to <30.0	1319 (39.5%)	1312 (38.6%)	1349 (39.3%)	1368 (40.5%)
Obese, ≥30.0	807 (24.1%)	910 (26.8%)	906 (26.4%)	969 (28.7%)
Smoking status				
Current smoker	878 (26.3%)	823 (24.2%)	904 (26.4%)	890 (26.3%)
Former smoker	1031 (30.8%)	1078 (31.8%)	1036 (30.2%)	1149 (34.0%)
Never smoker	1434 (42.9%)	1494 (44.0%)	1490 (43.4%)	1341 (39.7%)
Drinking status				
Current drinker	1931 (57.8%)	1837 (54.1%)	1925 (56.1%)	2086 (61.7%)
Former drinker	576 (17.2%)	620 (18.3%)	592 (17.3%)	612 (18.1%)
Never drinker	836 (25.0%)	938 (27.6%)	913 (26.6%)	682 (20.2%)
Physical activity score[2]	2.5 ± 0.8	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.8
Diabetes	270 (8.1%)	277 (8.2%)	317 (9.2%)	320 (9.5%)
Hypertension	902 (27.0%)	993 (29.2%)	960 (28.0%)	886 (26.2%)
Total serum cholesterol, mg/dL	215 ± 42.1	215 ± 41.3	215 ± 41.4	214 ± 41.6
Stage 2+ CKD, eGFR < 90 mL/(min·1.73 m^2)	492 (14.7%)	520 (15.3%)	558 (16.3%)	542 (16.0%)

[1] Baseline characteristics are reported as means ± SDs for continuous variables and *n* (%) for categorical variables. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[2] Physical activity score for sport-related exercise during leisure time.

Results

A total of 13,548 participants were included in the present study. The mean baseline age of participants was 54 y and 56% were women. The energy-adjusted average ultra-processed food intake was 6.0 servings/d (range: 0.1–28.8 servings/d). Beverages such as low-calorie and regular soft drinks and fruit-flavored punch or noncarbonated beverages (27%), fats and oils such as margarine (18%), and bakery goods such as ready-made pie, donuts, biscuits or cornbread, and danish pastry (15%) contributed the most to the frequency of ultra-processed food consumption in the study population (**Figure 1**).

Compared with participants in the lowest quartile, those in the highest quartile of frequency of ultra-processed food intake were more likely to be white, male, obese, and to have diabetes and stage 2+ chronic kidney disease (**Table 1**). The intake of ultra-processed foods was generally similar across the 4 study centers, with slightly higher intake in participants residing in the suburbs of Minneapolis, MN. Participants in the highest quartile of frequency of ultra-processed food intake had higher intakes of total fat, SFAs, MFAs, and PFAs, and sugar (**Table 2**). Dietary intake of protein, cholesterol, fiber, and micronutrients (e.g., folate, niacin, vitamin A, vitamin B6, vitamin B12, sodium, calcium, iron, phosphorus, magnesium, and potassium) were lower among participants in the highest quartile.

During a median follow-up of 27 y (312,266 person-years), a total of 2006 cases of incident CAD occurred. CAD incidence rate was 19.4% greater in the highest quartile (70.8 per 10,000 person-years; 95% CI: 65.1, 77.1) of ultra-processed food consumption compared with the lowest quartile (59.3 per 10,000 person-years; 95% CI: 54.1, 65.0). The cumulative incidence of CAD was higher for those in the highest quartile of ultra-processed food consumption compared with those in the lowest quartile throughout the follow-up period (**Figure 2**).

After adjusting for age, sex, race-center, and total energy intake (model 1), participants in the highest compared with those in the lowest quartile of ultra-processed food intake had a 21% higher risk of incident CAD (HR: 1.21; 95% CI: 1.06, 1.37; **Table 3**). After additional adjustment for socioeconomic status and health behaviors (smoking, drinking, physical activity) (model 2), those in the highest compared with the lowest quartile of ultra-processed food intake had a 19% higher risk of CAD (HR: 1.19; 95% CI: 1.05, 1.35).

There was an approximately linear relation between higher intake of ultra-processed food intake and the risk of incident CAD, particularly for those who consumed ≥4 servings of ultra-processed foods/d (**Figure 3**). For each additional serving of ultra-processed food intake >4.02 servings/d, there was a 3.2% higher risk of incident CAD (95% CI: 0.74, 5.74).

BMI, eGFR, and diabetes status were mediators of the association between ultra-processed food consumption and

TABLE 2 Nutritional characteristics according to quartiles of ultra-processed food consumption in the Atherosclerosis Risk in Communities Study[1]

Nutrient	Quartile 1 ($n = 3343$)	Quartile 2 ($n = 3395$)	Quartile 3 ($n = 3430$)	Quartile 4 ($n = 3380$)
Total energy, kcal/d	1690 ± 545	1490 ± 501	1520 ± 513	1740 ± 589
Protein, % of energy	19.7 ± 3.9	18.9 ± 3.5	17.7 ± 3.3	16.6 ± 3.5
Carbohydrate, % of energy	49.4 ± 8.8	49.1 ± 8.2	49.3 ± 8.2	48.9 ± 8.8
Total fat, % of energy	30.5 ± 6.4	32.1 ± 5.7	32.9 ± 5.6	34.1 ± 6.1
SFA, % of energy	11.1 ± 2.9	11.6 ± 2.6	11.8 ± 2.5	12.2 ± 2.6
MUFA, % of energy	11.7 ± 2.8	12.4 ± 2.6	12.9 ± 2.5	13.4 ± 2.7
PUFA, % of energy	4.5 ± 1.2	4.8 ± 1.1	5.0 ± 1.1	5.3 ± 1.3
Sugar, g/1000 kcal	65.2 ± 21.2	66.9 ± 20.9	68.8 ± 22.4	69.6 ± 25.5
Alcohol, g/d	7.0 ± 15.1	4.7 ± 10.1	5.0 ± 10.4	6.4 ± 14.2
Cholesterol, mg/1000 kcal	160 ± 59.3	161 ± 52.1	157 ± 54.2	145 ± 48.7
Folate, μg/1000 kcal	160 ± 50.0	157 ± 50.3	152 ± 50.5	145 ± 56.7
Niacin, mg/1000 kcal	12.8 ± 2.8	12.5 ± 2.7	11.8 ± 2.5	11.1 ± 2.7
Fiber, g/1000 kcal	12.3 ± 4.2	11.4 ± 3.6	10.5 ± 3.2	9.7 ± 3.0
Vitamin A, IU/1000 kcal	7270 ± 4830	6540 ± 3820	5760 ± 3690	4950 ± 3100
Vitamin B6, mg/1000 kcal	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	1.0 ± 0.3
Vitamin B12, μg/1000 kcal	4.9 ± 2.3	4.9 ± 2.4	4.5 ± 2.1	4.1 ± 2.0
Vitamin C, mg/1000 kcal	78.5 ± 38.5	80.1 ± 38.9	80.5 ± 40.4	77.8 ± 44.8
Vitamin E, mg/1000 kcal	3.2 ± 1.4	3.2 ± 1.4	3.1 ± 1.4	3.0 ± 1.5
Sodium, mg/1000 kcal	938 ± 190	927 ± 171	924 ± 176	919 ± 177
Calcium, mg/1000 kcal	458 ± 184	418 ± 164	390 ± 143	381 ± 144
Iron, mg/1000 kcal	7.3 ± 2.0	7.3 ± 2.1	7.2 ± 2.2	6.8 ± 2.2
Phosphorus, mg/1000 kcal	727 ± 145	687 ± 140	650 ± 138	639 ± 148
Magnesium, mg/1000 kcal	177 ± 37.1	165 ± 35.6	155 ± 33.9	148 ± 34.4
Zinc, mg/1000 kcal	6.8 ± 1.4	6.8 ± 1.4	6.6 ± 1.5	6.6 ± 1.7
Potassium, mg/1000 kcal	1820 ± 378	1730 ± 370	1630 ± 357	1546 ± 357

[1]Nutritional characteristics are reported as means ± SDs. IU, international units.

incident CAD, with diabetes status accounting for the largest proportion of the association between ultra-processed food and incident CAD (9.9% mediated; 95% CI: 2.0%, 32.0%; **Supplemental Table 2**).

The association between ultra-processed food and incident CAD was similar across subgroups by sex, race, BMI category, diabetes status, and hypertension status (**Figure 4**). Results were similar in sensitivity analyses when we excluded the first 2 y of follow-up and excluded CAD cases that occurred in the first 5 y of follow-up.

Discussion

In this large prospective study of middle-aged US adults, we observed a significant association between higher ultra-processed food intake and higher risk of incident CAD. We found an approximately linear association, which remained significant after adjusting for demographic, socioeconomic, and clinical factors. The results were consistent across subgroups by sex, race, BMI categories, hypertension status, and diabetes status.

Our findings are consistent with those of previous studies which used the NOVA framework to study the association between ultra-processed food consumption and cardiovascular disease. Specifically, in the French NutriNet-Santé cohort, researchers found that a 10% higher intake of ultra-processed food was associated with a 13% higher risk of overall CAD (15). A recent study from the Framingham Offspring cohort reporter a 9% higher risk of incident CAD for each additional daily serving of ultra-processed foods (32). Our findings on the nutritional characteristics of ultra-processed food were also in line with those of previous studies indicating that diets that were higher in ultra-processed foods consisted of a higher amount of fat and sugar and a lower amount of protein, fiber, and micronutrients (32–34). However, most of the prior studies were conducted in European populations (France, Spain) and comprised =predominately white, highly educated, younger adults, with dietary patterns that are likely to be distinct from those in the United States. On the other hand, studies of ultra-processed foods conducted in US populations have mostly been cross-sectional or consisted of only a small proportion of African-American or Hispanic participants, which limits the generalizability of the results (10, 33). Only 1 prospective study in the United States conducted in NHANES included a sizable proportion of different racial groups in addition to white participants (34). To the best of our knowledge, our study is the first to assess the prospective association between ultra-processed food intake and incident CAD in a diverse sample of US adults consisting of black and white participants.

There are several potential pathways which may explain the association between ultra-processed food consumption and CAD. From a nutrition standpoint, participants in the highest quartile of ultra-processed food consumption had a higher intake of total fat, saturated fat, and sugar, and lower intake of fiber, protein, and micronutrients. Previous studies have reported that excessive intakes of saturated fat and sugar were associated with a higher risk of obesity and diabetes, which are important cardiovascular disease risk factors (35, 36). In a recent study conducted in a large sample of Italian men and women, high sugar intake explained around 36% of the association between ultra-processed foods and cerebrovascular mortality (37).

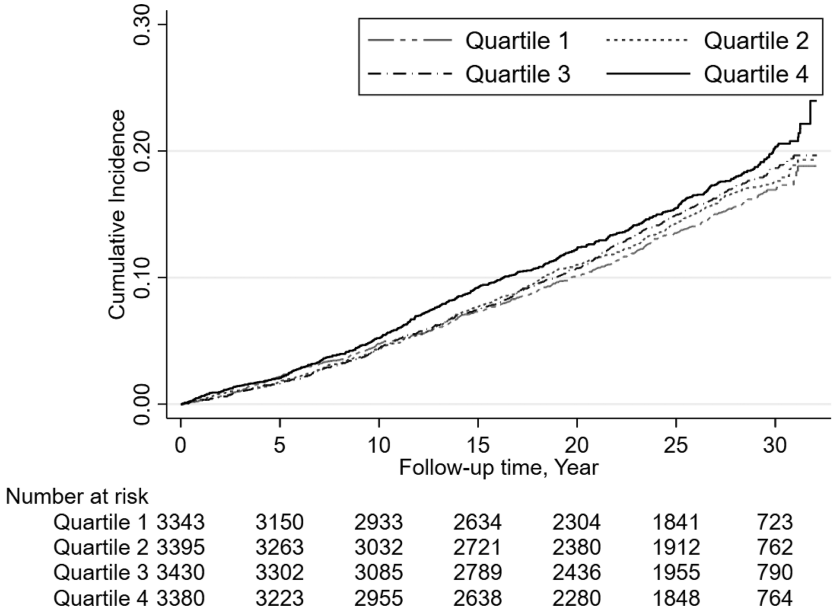

FIGURE 2 Kaplan-Meier estimate of cumulative incidence of coronary artery disease according to quartile of ultra-processed food consumption over 32 y of follow-up in the Atherosclerosis Risk in Communities Study.

Beyond nutritional factors, ultra-processed food intake may elevate the risk of CAD by introducing neo-formed contaminants during food processing. For example, acrylamide and acrolein are 2 compounds that are found to be associated with elevated CAD risk (38, 39). Processing of food can alter the structure of food, which influences its functionality and bioavailability of nutrients (40). The modified structure of foods in combination with their poor nutritional quality such as the low fiber content, are likely to facilitate faster eating rates and higher energy intakes through the alterations of satiety and glycemic responses, which have been linked to major cardiovascular disease risk factors such as obesity and diabetes (41, 42).

Food additives used in ultra-processed foods may also play a role in the elevated CAD risk observed in our study. Research has shown peptides γ-glutamylvaline and γ-glutamylisoleucine, which are often used in chicken broth products to induce the lasting savory taste, are found to be associated with diabetes and progression of arterial stiffness (43). Monosodium glutamate is another glutamate metabolite that is used as a food additive and has been shown to lead to atherosclerosis and other CADs in animal experiments (44). Some studies have indicated that excess dietary phosphorus consumption, especially inorganic phosphate, which is high in ultra-processed foods, is associated with vascular calcification and increased risk of other cardiovascular outcomes (45, 46). Noncaloric sweeteners such as acesulfame potassium have also been found to accelerate atherosclerosis in cellular models (47). Emulsifiers like carboxymethylcellulose may influence the gut microbiome environment and lead to low-grade gastrointestinal inflammation in animals (48). Lastly, environmental chemicals from plastic food packaging for ultra-processed foods also play an important role in elevating the risk of CAD. One study using data from a nationally representative sample of US adults in NHANES found that urine concentrations of certain phthalates and bisphenols (endocrine-disrupting chemicals linked to obesity and diabetes) were higher among those in the highest compared with those in the lowest quartile of ultra-processed food intake (49).

It is worth noting that lower intake of sodium and cholesterol was observed among those in the highest quartile of ultra-processed food consumption, which was in contrast with our expectation. However, similar results have been reported in other US population–based studies (33, 47). We suspect that the low sodium intake observed in our study may have been due to the less comprehensive documentation of sodium intake in the FFQ or underestimation of sodium intake in the food composition databases. As for cholesterol concentrations, there are many food items that are high in cholesterol (e.g., eggs, unprocessed beef, simple cheeses, plain yogurt, etc.) that were not classified as ultra-processed foods, which may explain the observed inverse relation between ultra-processed food intake and cholesterol concentrations (50).

Strengths of our study include the long-term follow-up, prospective study design which allowed us to establish temporality between ultra-processed food consumption and

TABLE 3 Incident coronary artery disease according to quartiles of ultra-processed food consumption in the Atherosclerosis Risk in Communities Study[1]

	Quartile 1 ($n = 3343$)	Quartile 2 ($n = 3395$)	Quartile 3 ($n = 3430$)	Quartile 4 ($n = 3380$)
Events observed, *n*	452	490	519	545
Model 1	1 [reference]	1.08 (0.95, 1.22)	1.12 (0.98, 1.27)	1.21 (1.06, 1.37)
Model 2	1 [reference]	1.05 (0.92, 1.19)	1.08 (0.95, 1.23)	1.19 (1.05, 1.35)

[1] Model 1 was adjusted for age, sex, race–center, and total energy intake. Model 2 was adjusted for the variables in model 1 plus education level, smoking status, drinking status, and physical activity score. Results are presented as hazard ratios (95% CIs) unless indicated.

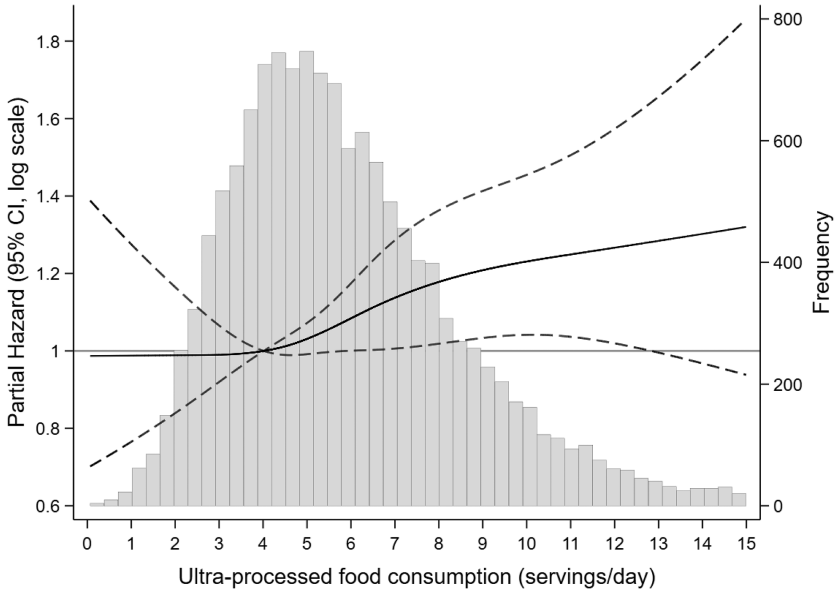

FIGURE 3 Partial hazard and 95% CIs for incident coronary artery disease according to intake of ultra-processed food/d using a restricted cubic spline in the Atherosclerosis Risk in Communities Study.[1] The gray histogram shows the distribution of ultra-processed food consumption. The black solid line represents the partial hazard for incident coronary artery disease, modeled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles. The reference level was set at the 25th percentile (4.02 servings/d). The black dashed lines represent 95% CIs. Partial hazard was adjusted for age, sex, race-center, total energy intake, education level, smoking and alcohol drinking status, and physical activity score.

incident CAD, large biracial sample of US adults to improve the external validity of the results, repeated measurements of dietary intake (visit 1 and 3) to account for within-individual variation, and rigorous ascertainment of CAD incidence.

There are also several limitations that need to be considered. First, the FFQ used in the present study was not specifically designed to answer food processing questions, and some common ultra-processed food items (e.g., energy bars, sports drinks) were not included. Second, misclassification errors can occur when classifying food items from the FFQ due to the lack of detailed information about food preparation and brands. However, there were similar trends in nutritional characteristics in our study compared with other studies that used 24-h dietary recalls, suggesting that we were able to rank participants according to frequency of consumption of ultra-processed foods reasonably well with the FFQ. Additionally, misclassification is likely nondifferential and biases our estimates toward the null. Third, despite many important confounders that we considered, residual confounding from unmeasured or imprecisely measured covariates cannot be ruled out. Last, the NOVA system has its own limitations, including lack of rigorous definition for processing levels and classification criteria that have been revised over time (51, 52). We decided to use the NOVA classification system to facilitate comparison with other studies, since it is the most commonly used framework.

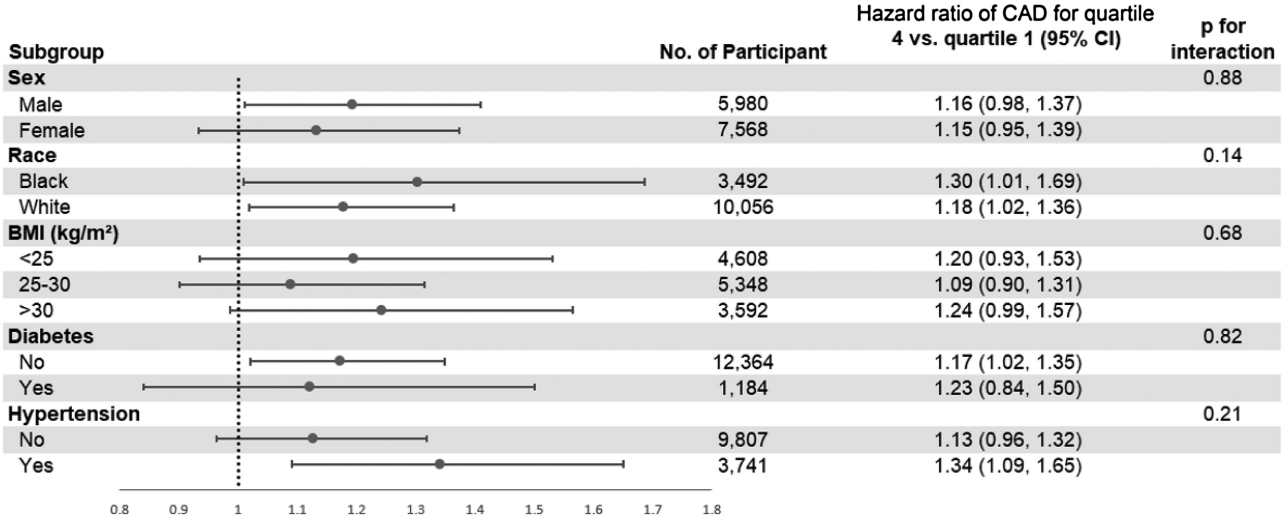

FIGURE 4 Subgroup analyses for the association between ultra-processed food consumption and incident coronary artery disease in the Atherosclerosis Risk in Communities Study.[1] The model was adjusted for age, sex, race–center, total energy intake, education level, smoking and alcohol drinking status, and physical activity score. CAD, coronary artery disease.

In conclusion, in this study of middle-aged US adults, higher ultra-processed food consumption was associated with a higher risk of CAD. Our findings confirm the association between ultra-processed food intake and cardiovascular disease found in other study populations. We expanded these findings by using data from a biracial cohort with similar results for black and white participants. Given the rise in ultra-processed food consumption and correlated trend in obesity in recent years, our study supports considering levels of food processing in national dietary guidelines. In addition, these findings provide justification for clinicians to advise their patients to limit consumption of ultra-processed food. Further research is necessary to confirm our results in longitudinal studies using a universally agreed upon ultra-processed food definition and classification system. It is warranted to further explore the relevant mechanisms underlying the association between ultra-processed foods and CAD.

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The authors' responsibilities were as follows—SD: designed the study, conducted data analysis, and drafted the manuscript; HK, CMR: contributed to data analysis, study planning, and manuscript revisions; and all authors: read and approved the final manuscript.

Data Availability

The code book and analytic code will be made available upon request pending application and approval from the Atherosclerosis Risk in Communities (ARIC) study. Data described in the manuscript will be made available upon request pending application and approval from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

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