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Original Research

Association of ultra-processed food consumption and MRI-based carotid plaque characteristics: results from the Atherosclerosis Risk in Communities study

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ABSTRACT

Background: Ultra-processed food and beverage consumption has been linked with adverse cardiovascular events, yet its association with sub-clinical disease remains less explored.
Methods: A total of 768 white participants from the Carotid MRI visit (2004–2005) in the Atherosclerosis Risk in Communities (ARIC) study were included. Participants were selected via stratified sampling to enrich for informative plaques while preserving population-level reference. Dietary intake was assessed using a 148-item food frequency questionnaire, with items classified by Nova processing levels. Carotid artery imaging was conducted via MRI and analyzed with semiautomated software. Weighted multivariable linear and logistic regression models assessed associations between quartiles of ultra-processed food intake and plaque measurements or lipid core presence.
Results: Higher ultra-processed food consumption was associated with unfavorable carotid plaque characteristics. Participants in quartile 4 of ultra-processed food consumption had greater total wall volume (standardized difference: β = 0.28, 95% CI, 0.07, 0.49), total lipid core volume (β = 0.55, 95% CI, 0.17, 0.92), maximum segmental wall thickness (β = 0.23, 95% CI, 0.01, 0.45), and maximum lipid core area (β = 0.49, 95% CI, 0.12, 0.86) vs. quartile 1. Replacing one daily serving of ultra-processed food with unprocessed or minimally processed food was associated with a reduction in total wall volume (β = -0.02, 95% CI, -0.05, -0.00).
Conclusions: Higher intake of ultra-processed food was associated with a greater burden of atherosclerotic plaque in the carotid artery. Our findings support the need for further investigation into the potential impact of ultra-processed food on atherosclerotic changes and the underlying mechanisms by which it may increase the future risk of cardiovascular disease development.

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Non-standard Abbreviations and Acronyms:

ARIC	Atherosclerosis Risk in Communities
UPF	Ultra-processed food
IMT	Intima media thickness
MRA	Magnetic resonance angiogram
DASH	Dietary Approaches to Stop Hypertension
AGEs	Advanced glycation end products
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid

1. Introduction

Ultra-processed foods are defined as foods that have undergone complex industrial processes, with the addition of non-culinary substances (e.g., emulsifiers, food colorants, preservatives) to enhance their appearance, taste, and shelf life. These foods are often calorie-dense, high in added sugar, fat, and salt, and low in protein, fiber, and micronutrients [1]. Previous evidence has linked ultra-processed food intake with several adverse health outcomes, including cardiovascular events [2–5]. While considerable research has been conducted between ultra-processed food and cardiovascular disease, the exact mechanisms remain less explored. One plausible pathway by which ultra-processed food increases cardiovascular risk is through atherosclerosis—a process involving the buildup of lipid-rich plaques in the arterial walls, which narrows the arteries and obstructs blood flow, thereby increasing the risk of stroke, myocardial infarction, and atherosclerotic cardiovascular disease [6].

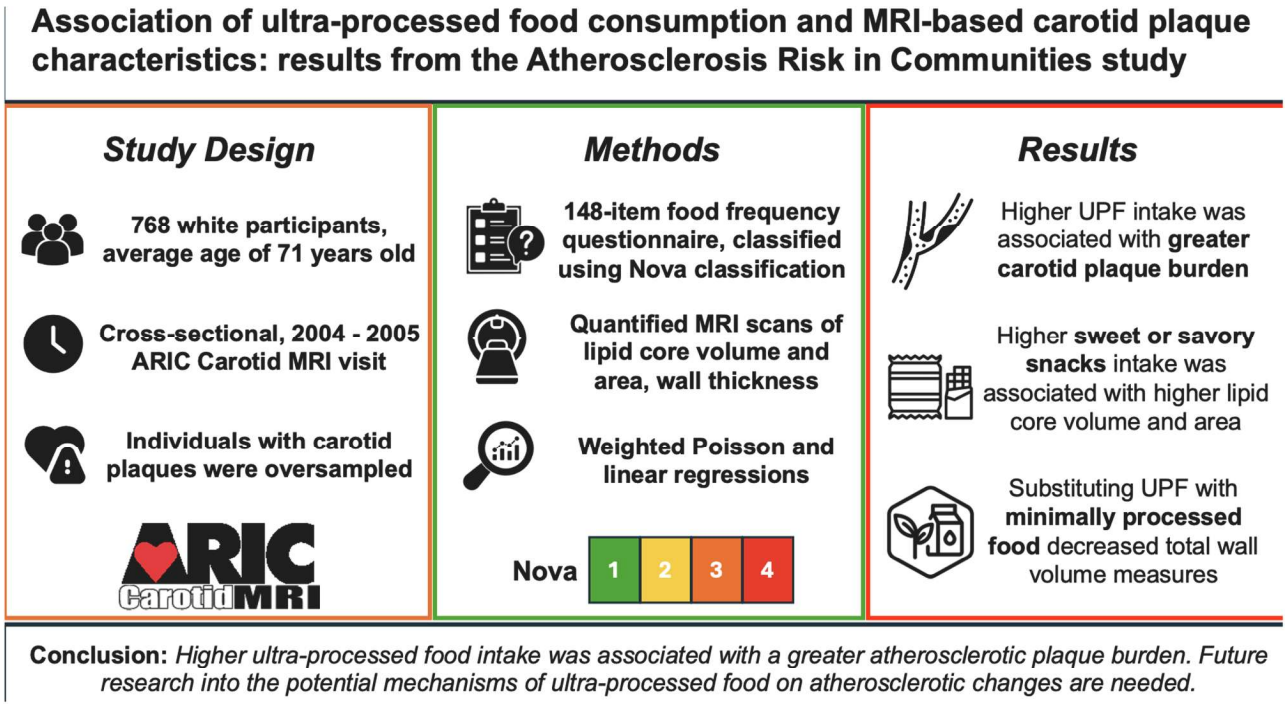
Magnetic resonance imaging (MRI) is a non-invasive imaging technique that utilizes a magnetic field and radio waves to generate high-resolution images of internal anatomical structures. Advancements in MRI have enabled vessel wall imaging, a specialized approach that enhances the visualization of arterial walls and atherosclerotic plaques. This represents a significant breakthrough in cardiovascular imaging, allowing for detailed characterization of plaque burden and composition. Previous studies have found that MRI-based measures of plaque characteristics, such as lipid core presence, lipid core volume, and carotid wall thickness, are associated with future cardiovascular disease events [7–9]. Understanding the association between ultra-processed food intake and vascular measures can help generate hypotheses about potential mechanisms, which may, in turn, inform future prevention strategies aimed at reducing cardiovascular disease risk through dietary modification.

In the current study, we aimed to investigate cross-sectional associations between ultra-processed food consumption and carotid plaque characteristics measured by MRI in men and women participating in the Atherosclerosis Risk in Communities (ARIC) Carotid MRI substudy. We hypothesized that a higher intake of ultra-processed food was associated with a greater burden of carotid plaques.

2. Methods

2.1. Study population

The ARIC study is a prospective, population-based cohort study of 15,792 mostly black and white participants aged from 45 to 64 years at baseline visit (1987 - 1989). All participants were recruited from four U.S. communities: Forsyth County, North Carolina; Minneapolis subways, Minnesota; Jackson, Mississippi; and Washington County, Maryland [10]. During study visits, a B-mode ultrasound examination was performed to measure participants' carotid artery intima media thickness (IMT). In 2004–2005, a subsample of participants who had previously undergone an ultrasound examination was re-examined during the ARIC Carotid MRI study visit [11]. A stratified sampling strategy was employed based on previously documented ultrasound measures from visit 3 (1993 - 1995) and visit 4 (1996 - 1998), with the goal of oversampling participants with carotid plaques. The sampling process involved two groups: (1) 1250 participants with a carotid artery IMT (maximum value over 6 measured sites: left and right of the common and internal carotid arteries, and carotid bifurcation) above the 68th percentile of the population (field center specific cut-offs were used to ensure that a similar number of participants were selected from each center); (2) 816 individuals randomly selected from the remaining IMT



Central illustration: Higher intake of ultra-processed food was associated with a greater burden of atherosclerotic plaque in the carotid artery.

distribution. In total, 2066 participants with previous carotid artery ultrasound examinations were enrolled and participated in the ARIC Carotid MRI visit. The study protocol was reviewed and approved by the institutional review board at each center, and all participants provided written informed consent.

For the current analysis, we excluded participants from the Jackson and Forsyth County field centers that did not collect dietary intake data ($n = 966$), people with more than 8 food items missing from the food frequency questionnaire ($n = 1$), and those with implausible energy intake (defined as less than 500 or more than 3500 kcal per day for women, and less than 600 or more than 4500 for men) ($n = 4$). We further excluded participants with missing covariates ($n = 22$), missing MRI exam measurements ($n = 149$), and those who reported a previous history of coronary heart disease ($n = 156$). The final analytical sample was 768 (Fig. S1).

2.2. Dietary intake and ultra-processed food classification

Dietary intake was recorded during the interview portion of the participant's visit, and was assessed using a 148-item validated, modified version of the Willett food frequency questionnaire [12]. Trained clinic staff administered the questionnaire by asking participants to report how often on average they ate a specific portion of each food item in the past year. Reported intake of each food item was multiplied by the nutritional content (obtained from the US Department of Agriculture Food and Nutrient Database for Diet Studies) to calculate average daily nutrient intakes.

Food items were classified into one of four distinct processing levels according to the Nova classification system: (1) unprocessed or minimally processed foods, which include foods obtained directly from nature and subjected to no or minimal processing, such as grinding, freezing, or pasteurizing; (2) processed culinary ingredients, which are derived from whole foods and used to season or cook, including oils, butter, sugar, and salt; (3) processed foods, which are made by combining group 1 and group 2 foods, typically for preservation or to make them more palatable; and (4) ultra-processed foods, which are industrial formulations made entirely or mostly from derived substances, containing little to no intact whole foods in their original form [13]. A total of 148 food items were classified into one of four categories. Two coders independently classified all food items initially, and a third coder reviewed and resolved any discrepancies between their classifications (Table S1). Ultra-processed food items were then further grouped into one of the following ten categories: animal-based foods, baked goods and grains, cereals, dairy foods, fried foods, hard liquor, margarine, ultra-processed drinks, ultra-processed condiments, and sweet or savory snacks.

Total ultra-processed food consumption, calculated as the summed frequency of all ultra-processed food items in servings per day, was regressed on total energy intake. The residuals, calculated as the differences between the predicted and observed values for each participant, were then ranked to categorize participants into energy-adjusted quartiles of ultra-processed food intake [14].

2.3. MRI protocol and image analysis

All participants underwent a standard MRI protocol and were examined on 1.5T scanners (either Excite platform, GE Medical Systems, or Symphony Maestro, Siemens Medical Solutions) equipped with bilateral four channel phased array carotid coils (Machnet). The protocol began with a 3D time-of-flight magnetic resonance angiogram (MRA) to image both carotid bifurcations. Detailed black-blood MRI images were then taken, focusing on the side of the carotid artery with the thicker wall, or on the opposite side if it appeared more narrowed or stenotic. These images were aligned perpendicular to the artery and centered at the thickest part of the wall, capturing the area of interest in parallel slices. A 3D contrast-enhanced MRA was then performed with the injection of gadodiamide (Omniscan, GE Healthcare) to better delineate the lumen. Five minutes post-injection, additional black-blood MRI images were repeated with adjusted inversion times for enhanced contrast, covering 3.2 cm with 16 transverse slices through the carotid bifurcation area. All scans were conducted by 14 certified technologists with extensive training and were validated through the ARIC MRI Reading Center [11].

Seven readers with a minimum of three months of training interpreted MRI images while masked to participant characteristics. Readers assigned quality scores of 0, 1, or 2 to each exam based on image clarity and adherence to protocol. Failed exams (score = 0) were excluded. Analysis was performed on eight slices that were centered at the thickest wall slice with matching pre- and post- contrast images. On post-contrast images, readers drew contours of lumen, lipid core, outer vessel wall, and any calcification, which were used to calculate measurements of plaque components [15,16]. Semiautomated analysis software (VesselMASS; Leiden University Medical Center) then divided the imaged vessel walls into 12 radial segments and fibrous caps at 15-degree increments. Thickness and area measurements were calculated within each slice, and volumetric data were derived by integrating these area values over the eight contiguous slices [17]. Detailed examples of MRI imaging and measurement techniques are described in prior publications [18,11,8].

Our outcomes of interest were: (1) total wall volume (mm^3), computed by combining area measurements over all eight examined slices; (2) total lipid core volume (mm^3), computed by combining lipid-rich core area measurements over all eight examined slices; (3) maximum segmental wall thickness (mm), the thickest artery wall of 12 segments at the slice with the largest lipid contour area; (4) maximum lipid core area (cm^2), the largest lipid-rich core area measurements over the eight slices; and (5) lipid core presence, a binary variable indicates the presence or absence of a lipid core at any of the eight slices. For the analysis of lipid core presence, we restricted the sample to participants with a maximum wall thickness $\geq$1.5 mm ($n = 553$) due to MRI resolution constraints. The prevalence of lipid core presence in the analytic sample was 40.9 % ($n = 226$). The reliability and variability of these measurements have been previously evaluated [11].

2.4. Assessment of covariates

Participant characteristics, including age, race, sex, education level, smoking status, drinking status, and physical activity score, were collected through interviews conducted by trained clinic staff at each field center. Education level was categorized into one of the three following: lower than high school (less than completed high school), high school equivalent, and higher than high school (at least some college). Height and weight were measured on site and used to calculate body mass index. Physical activity score was calculated using a modified version of the Baecke physical activity questionnaire [19]. Estimated glomerular filtration rate (eGFR) was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without the consideration of race (using age, sex, and serum creatinine) [20]. Participants were considered to have hypertension if they had a diastolic blood pressure of 90 mmHg or more, or a systolic blood pressure of 140 mmHg or more, or used anti-hypertensive medication within the past two weeks. Participants were considered to have diabetes if they met any of the following criteria: a fasting glucose level higher than 126 mg/dL, a non-fasting glucose level higher than 200 mg/dL, self-reported previous physician diagnosis of diabetes, or use of diabetes or blood sugar-lowering medications within the four weeks preceding the study visit.

2.5. Statistical analysis

All analyses (excluding participant and nutritional characteristics) accounted for the stratified sampling design of the Carotid MRI visit by

weighting by the inverse of the sampling probabilities of being selected from each center and IMT stratum. Unweighted participant and nutritional characteristics were presented and compared across quartiles of energy-adjusted ultra-processed food consumption. Continuous variables were reported as mean ± standard deviation, while categorical variables were presented as number (percentage). P-values were calculated using the Pearson's chi-square test for categorical variables and analysis of variance for continuous variables.

For the main analyses, weighted linear and Poisson regression with robust variance (due to the high prevalence of lipid core presence) were used to model associations between ultra-processed food intake and plaque measurements. Continuous dependent variables (total wall volume, total lipid core volume, maximum segmental wall thickness, maximum lipid core area) were standardized by dividing the standard deviations of the entire sample, and the coefficients represent the standardized differences in plaque measurements comparing quartile 4 to quartile 1 of ultra-processed food intake. For the binary dependent variable (lipid core presence), the coefficient represents the odds ratio for the presence of a lipid core comparing quartile 4 to quartile 1, approximated using Poisson regression with robust standard errors. To test for a linear trend across quartiles of ultra-processed food intake, we used the median value of each quartile as a continuous variable in the model to obtain a p-trend. Additionally, ultra-processed food intake was modeled as a continuous variable and measures of association were expressed per one additional serving per day of ultra-processed food. We tested the associations in three progressively adjusted models. Model 1 was unadjusted. Model 2 adjusted for age, sex, total energy intake, drinking and smoking status, physical activity score, and education level. Model 3 further adjusted for hypertension, diabetes, and kidney function (eGFR levels modeled with two linear spline segments, with a knot at 90 mL/min/1.73 m^2). For analyses of lipid core presence, all models additionally adjusted for maximum wall thickness. Model 3 was considered as the main model in our study. All covariates were tested for collinearity using the variance inflation factor (VIF), and all VIF values were below 5, indicating no substantial collinearity.

For the main model, we usually examined the associations between ultra-processed food intake (servings per day) and four continuous plaque measurements using restricted cubic spline curves with four knots set at the 5th, 35th, 65th, and 95th percentiles [21].

We explored the associations between specific ultra-processed food groups and plaque measurements by calculating energy-adjusted intake, ranking participants, dividing them into quartiles for each food group, and generating coefficients while controlling for covariates from the main model and the consumption of other food groups.

We assessed associations between unprocessed or minimally processed food intake and plaque measurements, analyzing both categorical and continuous intake, following the same approach used in the main analysis. We also performed substitution analysis estimating the impact of replacing ultra-processed food with unprocessed or minimally processed food [22].

We conducted two sets of sensitivity analyses. First, we adjusted for participants' intake of unprocessed or minimally processed foods, processed culinary ingredients, and processed foods, in addition to the covariates included in Model 3, creating a new separate model. Second, we adjusted for participants' lipid profiles, including total cholesterol, triglycerides, and HDL-cholesterol levels, alongside the covariates from Model 3, as another separate model.

3. Results

The mean age of participants at baseline was 71 years, 55 % were female, and all participants were white. The mean BMI was 28 kg/m^2. Sixty percent were current drinkers, and 9 % were current smokers. Seventeen percent of participants had prevalent diabetes, and 63 % had hypertension. Compared to the lowest quartile, participants in the highest quartile of ultra-processed food consumption tended to be less physically active, had lower education levels, were more likely to be former drinkers and to have diabetes (Table 1). On average, participants in quartile 4 consumed 11.1 servings of ultra-processed food per day, compared to 4.5 servings/day in quartile 1. Participants in quartile 1 consumed 14.4 servings of unprocessed or minimally processed food per day, while those in quartile 4 consumed 11.2 servings/day.

Higher ultra-processed food intake was associated with lower intakes of protein, fiber, cholesterol, and certain micronutrients (magnesium, phosphorus, potassium, vitamin A, vitamin C, vitamin D), and higher intake of sodium (Table 2). Participants in the highest quartile of ultra-processed food consumed more sugar-sweetened beverages and fewer whole fruits, vegetables, legumes, and alcohol drinks compared to those

Table 1
Baseline characteristics of ARIC Carotid MRI participants by consumptions of ultra-processed food in quartiles.[a]

Variables	Quartile 1 (*n* = 192)	Quartile 2 (*n* = 192)	Quartile 3 (*n* = 192)	Quartile 4 (*n* = 192)	P-value
Range of adjusted ultra-processed food intake, servings/day	0.0 – 5.6	5.6 – 7.1	7.1 – 8.9	8.9 – 20.6	–
Adjusted ultra-processed food intake, servings/day	4.5 ± 1.0	6.4 ± 0.4	7.9 ± 0.5	11.1 ± 2.1	<0.001
Adjusted minimally processed food intake, servings/day	14.4 ± 4.4	12.1 ± 3.5	12.2 ± 3.5	11.2 ± 3.6	<0.001
Age, years	71.0 ± 5.5	70.6 ± 5.1	71.4 ± 5.7	71.0 ± 5.5	0.51
Female sex	95 (49.5 %)	117 (60.9 %)	113 (58.9 %)	96 (50.0 %)	0.04
Body mass index, kg/m^2	27.7 ± 4.2	28.2 ± 4.4	28.6 ± 5.0	29.0 ± 5.0	0.04
Physical activity score[b]	2.9 ± 0.8	2.8 ± 0.8	2.8 ± 0.8	2.7 ± 0.9	0.05
Education level					
Lower than high school	15 (7.8 %)	21 (10.9 %)	26 (13.5 %)	33 (17.2 %)	0.04
High school equivalent	67 (34.9 %)	75 (39.1 %)	80 (41.7 %)	70 (36.5 %)	
Higher than high school	110 (57.3 %)	96 (50.0 %)	86 (44.8 %)	89 (46.4 %)	
Smoking status					
Current	15 (7.8 %)	12 (6.2 %)	16 (8.3 %)	23 (12.0 %)	0.22
Former	86 (44.8 %)	83 (43.2 %)	82 (42.7 %)	94 (49.0 %)	
Drinking status					
Current	134 (69.8 %)	113 (58.9 %)	100 (52.1 %)	113 (58.9 %)	0.002
Former	28 (14.6 %)	55 (28.6 %)	57 (29.7 %)	56 (29.2 %)	
eGFR, mL/min per 1.73 m^2	80.5 ± 16.1	78.1 ± 15.2	78.7 ± 15.9	80.1 ± 15.9	0.41
Diabetes status	24 (12.5 %)	35 (18.2 %)	37 (19.3 %)	61 (31.8 %)	<0.001
Hypertension status	117 (60.9 %)	113 (58.9 %)	130 (67.7 %)	125 (65.1 %)	0.27
Total cholesterol, mg/dL	199.0 ± 45.1	195.7 ± 41.4	194.5 ± 42.0	189.7 ± 38.5	0.18
Triglycerides, mg/dL	146.3 ± 81.7	161.8 ± 90.7	157.3 ± 100.0	157.0 ± 82.3	0.37
HDL-cholesterol, mg/dL	51.0 ± 13.9	49.3 ± 14.3	49.3 ± 14.3	48.0 ± 14.9	0.23

[a] Statistics reported are mean ± standard deviation for continuous variables and n (%) for categorical variables.

[b] Physical activity score ranges from 1 to 5, reflects activity during leisure time, and incorporates frequency, duration, and intensity of activity.

Table 2
Nutritional characteristics of ARIC Carotid MRI participants by consumptions of ultra-processed food in quartiles.

	Quartile 1 (n = 192)	Quartile 2 (n = 192)	Quartile 3 (n = 192)	Quartile 4 (n = 192)	P-value [a]
Total energy intake, kcal/day	1867.9 ± 534.7	1600.8 ± 613.1	1651.3 ± 623.8	1821.0 ± 548.4	<0.001
Macronutrient intake, per 1000 kcal					
Carbohydrate, g	118.9 ± 21.3	122.9 ± 19.2	122.9 ± 19.2	121.5 ± 19.8	0.2
Protein, g	45.3 ± 8.6	42.6 ± 7.1	41.9 ± 7.8	41.0 ± 7.5	<0.001
Total fat, g	37.7 ± 7.2	38.6 ± 7.0	38.3 ± 6.6	39.1 ± 6.6	0.3
Saturated fat, g	11.6 ± 2.8	12.2 ± 2.6	12.1 ± 2.4	12.1 ± 2.4	0.07
Monounsaturated fat, g	14.7 ± 3.5	14.6 ± 3.2	14.2 ± 2.9	14.5 ± 2.9	0.5
Polyunsaturated fat, g	7.1 ± 2.1	7.1 ± 2.1	7.1 ± 2.1	7.6 ± 2.0	0.06
Total sugars, g	55.8 ± 15.9	58.7 ± 16.0	57.1 ± 15.7	53.8 ± 15.7	0.02
Dietary fiber, g	11.9 ± 4.1	10.9 ± 3.1	10.5 ± 2.9	10.4 ± 3.1	<0.001
Micronutrient intake, per 1000 kcal					
Sodium, mg	1072.5 ± 188.1	1165.3 ± 217.0	1219.0 ± 259.7	1309.1 ± 274.3	<0.001
Calcium, mg	662.2 ± 360.5	706.2 ± 432.8	675.5 ± 403.4	618.6 ± 350.5	0.2
Cholesterol, mg	153.2 ± 52.6	142.3 ± 40.7	139.4 ± 38.3	132.9 ± 44.8	<0.001
Iron, mg	13.0 ± 14.3	11.2 ± 9.2	11.8 ± 10.5	11.6 ± 9.6	0.5
Magnesium, mg	223.2 ± 70.9	204.1 ± 59.5	200.0 ± 67.8	193.8 ± 74.8	<0.001
Phosphorous, mg	760.3 ± 140.0	712.3 ± 121.0	701.3 ± 138.8	688.2 ± 122.2	<0.001
Potassium, mg	1792.5 ± 327.9	1697.2 ± 340.3	1641.2 ± 344.7	1563.4 ± 306.5	<0.001
Zinc, mg	13.4 ± 9.1	12.4 ± 8.9	11.4 ± 8.0	13.3 ± 12.2	0.1
Niacin, mg	21.5 ± 12.5	20.3 ± 10.8	20.1 ± 12.4	20.6 ± 13.0	0.7
Folate, μg	395.5 ± 195.7	391.8 ± 213.0	361.5 ± 223.5	357.7 ± 173.4	0.1
Vitamin A, IU	7809.9 ± 4852.2	6744.5 ± 3904.6	5851.9 ± 3026.6	5831.5 ± 3378.3	<0.001
Vitamin C, mg	233.3 ± 325.2	166.1 ± 180.8	189.2 ± 246.3	158.3 ± 219.7	0.02
Vitamin B6, mg	5.4 ± 13.9	5.2 ± 17.5	5.7 ± 23.1	4.0 ± 10.9	0.8
Vitamin B12, μg	10.0 ± 10.5	10.2 ± 9.4	9.0 ± 9.4	9.5 ± 10.1	0.6
Vitamin D, IU	298.0 ± 206.1	322.6 ± 241.1	268.0 ± 214.3	250.1 ± 180.1	0.004
Food consumption, servings per day					
Dairy food	2.7 ± 2.0	2.3 ± 1.7	2.4 ± 2.0	3.0 ± 2.6	0.007
Whole fruits	1.8 ± 1.1	1.3 ± 0.8	1.2 ± 0.9	1.2 ± 0.8	<0.001
Vegetables and legumes	3.4 ± 2.0	2.4 ± 1.4	2.4 ± 1.3	2.3 ± 1.3	<0.001
Red meat	0.8 ± 0.5	0.8 ± 0.5	0.8 ± 0.4	0.8 ± 0.5	0.5
Sugar-sweetened beverages	0.3 ± 0.4	0.5 ± 0.7	0.7 ± 0.7	1.4 ± 1.4	<0.001
Alcohol drinks	0.8 ± 1.5	0.4 ± 0.8	0.5 ± 0.8	0.5 ± 1.0	0.001

Nutritional characteristics are reported as mean ± standard deviation. Abbreviations: IU, international units; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

[a] P values were calculated from analysis of variance for continuous variable.

in the lowest quartile.

Baked goods and grains (white and dark bread, pizza, and ready-made cookies and pastries) were the largest contributors to ultra-processed food consumption in this population, accounting for 34 % of total intake (Fig. 1). Ultra-processed condiments, such as low-fat mayonnaise, regular mayonnaise, and salad dressing, comprised 14 % of ultra-processed food consumption. Sweet or savory snacks, including chocolate candy bars, popcorn, and jams, as well as ultra-processed drinks like diet sodas and sugary beverages, each contributed 10 %. Dairy foods (e.g., flavored yogurt and ice cream) accounted for 9 %, while margarine and cereal contributed 8 % and 6 %, respectively.

In model 3, our main model, higher ultra-processed food consumption was significantly associated with higher total wall volume (β for quartile 4 vs. quartile 1 = 0.28; 95 % CI, 0.07, 0.49; p-trend = 0.02), total lipid core volume (β = 0.55; 95 % CI, 0.17, 0.92; p-trend = 0.01), maximum segmental wall thickness (β = 0.23; 95 % CI, 0.01, 0.45; p trend = 0.05), and maximum lipid core area (β = 0.49; 95 % CI, 0.12, 0.86; p-trend = 0.02), after adjusting for age, sex, total energy intake, drinking and smoking status, physical activity score, education level, hypertension status, diabetes status and kidney function (Fig. 2; Table 3). There was no significant association between ultra-processed food intake and lipid core presence.

In the continuous analysis, each additional serving of ultra-processed food was significantly associated with greater total wall volume (β = 0.03; 95 % CI, 0.00, 0.05; p = 0.03) and total lipid core volume (β = 0.06; 95 % CI, 0.01, 0.11; p = 0.02) in model 2, but not with maximum segmental wall thickness, maximum lipid core area, or lipid core presence (Table 3). When further adjusting for comorbidities including diabetes status, hypertension status, and kidney function, each additional serving of ultra-processed food was significantly associated only with greater lipid core volume (β = 0.06; 95 % CI, 0.01, 0.11; p = 0.03). The relationship between ultra-processed food consumption and all four continuous outcome measurements appeared to be linear (Fig. 3).

Higher consumption of unprocessed or minimally processed foods was significantly associated lower total wall volume in the unadjusted model; no other significant associations were found between unprocessed or minimally processed foods and carotid MRI measures (Table S2).

In the exploratory analysis of ultra-processed food groups, we found that higher consumption of sweet or savory snacks was associated with greater total lipid core volume (β = 0.45; 95 % CI, 0.10, 0.79; p-trend = 0.003) and maximum lipid core area (β = 0.44; 95 % CI, 0.07, 0.80; p trend = 0.01) (Fig. S2).

Substituting one serving of ultra-processed food with minimally processed food resulted in a statistically significant lower total wall volume measurement (β = -0.02; 95 % CI, -0.05, -0.00; p = 0.04), but not in other carotid MRI measures.

In the sensitivity analyses, after additionally adjusting for participants' intake of unprocessed or minimally processed foods, processed culinary ingredients, and processed foods, or for lipid profiles including total cholesterol, triglycerides, and HDL-C levels, both alongside the covariates in Model 3, the results remained consistent with those of the main model.

4. Discussion

In this study of 798 older men and women, higher consumption of ultra-processed food was associated with a greater atherosclerotic plaque burden, as indicated by MRI measures of total wall volume, total lipid core volume, maximum segmental wall thickness, and maximum lipid core area. The association persisted, even after accounting for sociodemographic characteristics, health behaviors, and clinical conditions. We found that the sweet or savory snacks subgroup of ultra processed food contributed to the association between higher intake and greater total lipid core volume and maximum lipid core area; and replacing one serving of ultra-processed food with unprocessed or minimally processed food has a favorable impact on total wall volume.

There is extensive evidence on the association between ultra processed food intake and cardiovascular disease risk [23]. A recent meta-analysis of 22 prospective studies on ultra-processed food and cardiovascular disease risk found that the highest category of

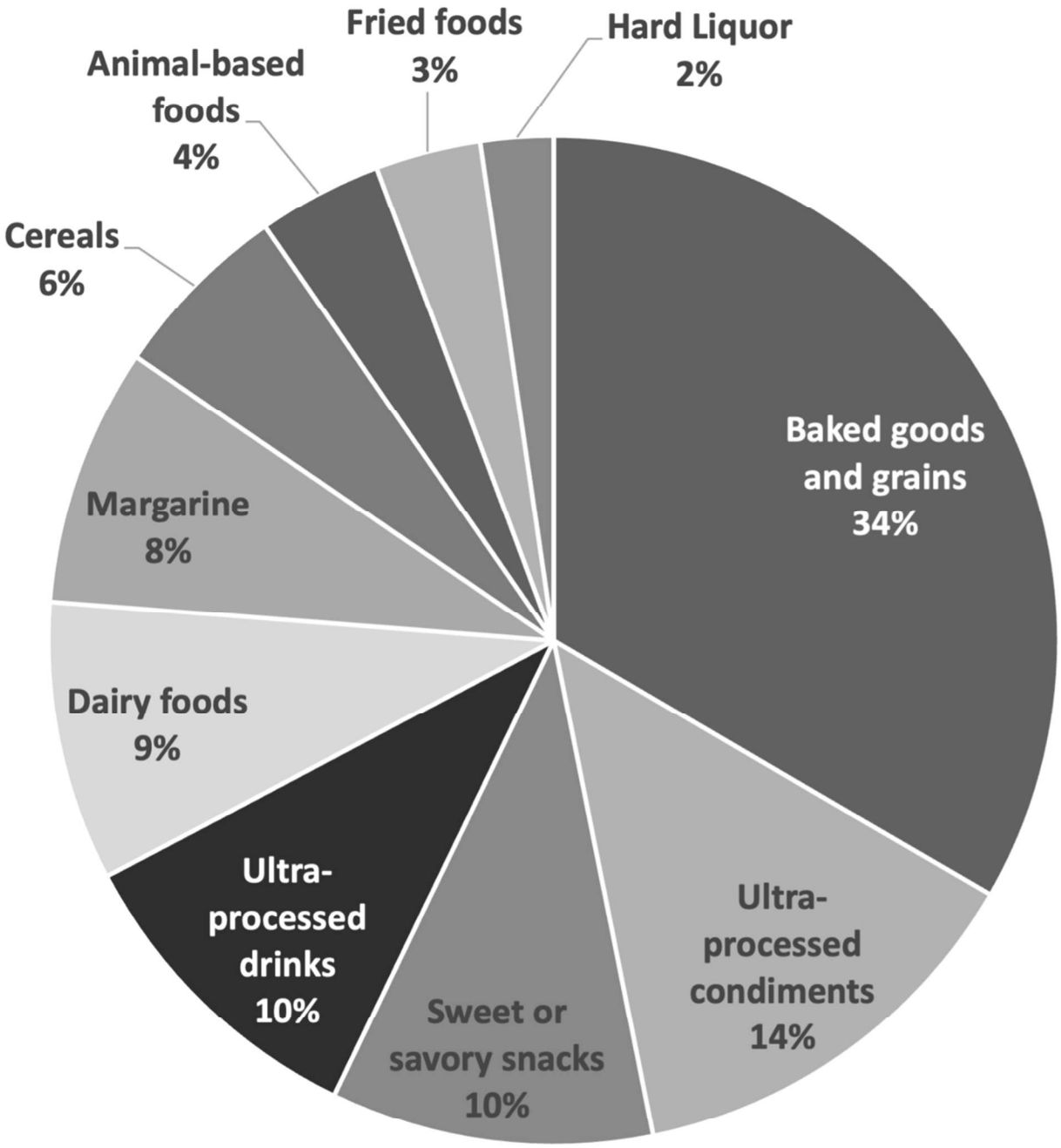


Fig. 1. Proportion (%) of each food group contributing to the frequency (servings/d) of ultra-processed food consumption in the Atherosclerosis Risk in Communities MRI Study.
Dairy foods: Non-dairy coffee whitener, Frozen yogurt, sherbet, or non-fat ice cream; Ice cream, Flavored yogurt, without Nutrasweet; Yogurt, plain or with Nutrasweet; Cream cheese; **Animal-based foods:** Egg Beaters or egg whites only; Beef or pork hot dogs, Chicken or turkey hot dogs, Salami, bologna, or other processed meat sandwiches; Processed meats (e.g., sausage, kielbasa, etc.), Store brought breaded fish cakes, pieces, or fish sticks; **Baked goods and grains:** White bread (slice), including pita bread; Dark bread (slice), including wheat pita bread; Bagels, English muffins, or rolls; Muffins (regular) or biscuits, Pancakes or waffles, Crackers, Triskets, Wheat Thins; Pizza, Pretzels, Cookies, ready made; Brownies, Doughnuts, Cake, ready made; Pie, ready made; Sweet roll, coffee cake, or other pastry, ready made; **Fried foods:** French fried potatoes, Potato chips or corn chips, Fried food away from home or as takeout (e.g., french fries, fried chicken, fish, clams, shrimp, etc.) **Ultra-processed drinks:** Low calorie cola (e.g., Diet Coke with caffeine), Low-calorie caffeine-free cola, Other low calorie carbonated beverage (e.g., Diet 7-Up, Fresca, diet ginger ale), Coke, Pepsi, or other cola with sugar; Caffeine-Free Coke, Pepsi, or other cola with sugar; Other carbonated beverage with sugar (e.g., 7-Up), Hawaiian Punch, lemonade, or other non-carbonated fruit drinks; **Sweet or savory snacks:** Pure chocolate candy bar or packet (e.g., Hershey's, M&M's), Other mixed candy bars (e.g., Snickers, Milky Way, Reeses), Candy without chocolate, Jams, jellies, preserves, syrup, or honey, Popcorn; **Ultra-processed condiments:** Nutrasweet or Equal, Low fat mayonnaise/fat free mayonnaise, Regular mayonnaise, Salad dressing, Ketchup or red chili sauce

ultra-processed food consumption was associated with a 9 % to 23 % higher risk of cardiovascular disease, coronary heart disease, and stroke, with the meta-evidence for coronary heart disease ranked as high [4]. Another dose-response meta-analysis of 20 studies, involving over 1 million participants, revealed a consistent linear relationship between ultra-processed food intake and cardiovascular events [24]. Despite the consistent evidence from population-based observational studies, the exact biological mechanisms by which ultra-processed food impacts

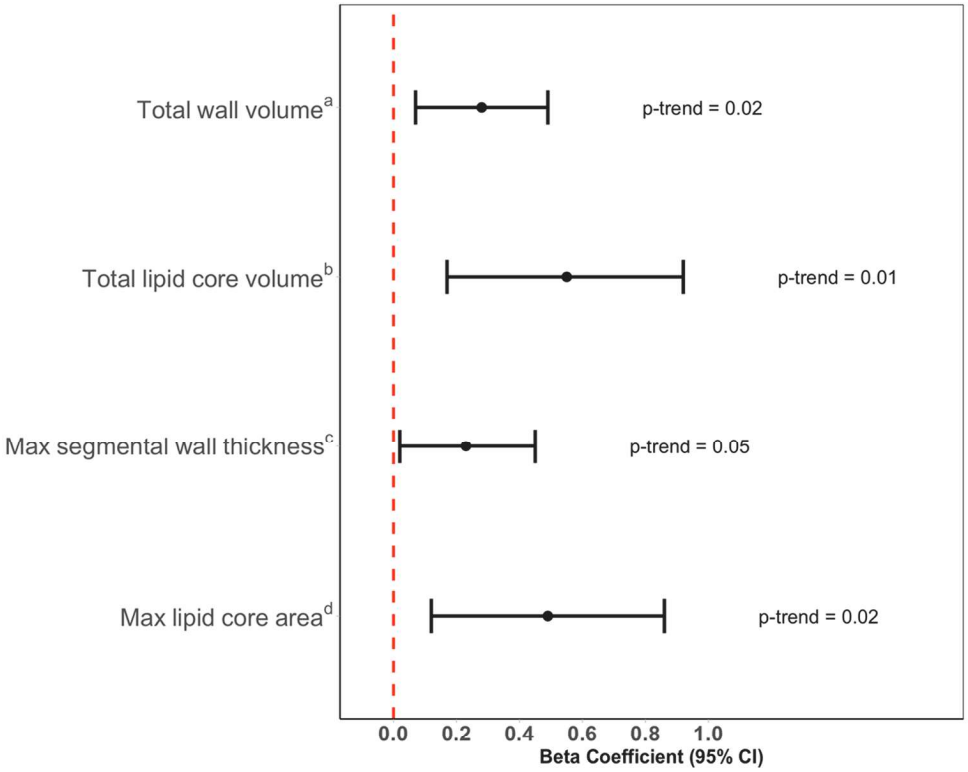


Fig. 2. Associations between measures of plaque characteristics and ultra-processed food consumption in quartiles.
The model was adjusted for age, sex, total energy intake, drinking status, smoking status, physical activity score, education level, hypertension status, diabetes status and kidney function (two linear spline terms with one knot at 90 mL/min/1.73 m^2). Coefficients for total wall volume, total lipid core volume, maximum segmental wall thickness, and maximum lipid core area represent the standardized differences in plaque measurements when comparing quartile 4 to quartile 1 of ultra-processed food intake; coefficients for lipid core presence represent the odds ratio for the presence of a lipid core comparing quartile 4 to quartile 1, approximated using Poisson regression with robust standard errors. [a] Total wall volume (in mm^3) was computed by integrating area measurements over 8 slices. [b] Total lipid core volume (in mm^3) was computed by integrating lipid-rich core area measurements of the 8 slices. [c] Maximum segmental wall thickness (in mm) was defined as the maximum wall thickness of 12 segments at the slice with the largest lipid contour area. [d] Maximum lipid core area (in cm^2) was computed by integrating lipid-rich core area measurements of the 8 slices.

cardiovascular risk require further clarification. Ultra-processed foods might exert their effects through traditional risk factors, including excessive weight gain, elevated blood pressure, kidney damage, dysregulated glycemic response, and changes in plasma lipid profiles, or through other potential mechanisms, such as altered gut microbiome composition and disruptions in endocrine pathways [25]. In the current study, we demonstrated the biological plausibility of ultra-processed food contributing to cardiovascular disease through the buildup of plaque in the carotid artery. Notably, the associations between ultra-processed food intake and carotid plaque characteristics remained significant even after adjusting for clinical factors including diabetes, hypertension, and kidney function. This suggests that the association between ultra-processed food and carotid plaques may not be fully explained by these traditional cardiovascular risk factors and could involve additional pathways that directly influence atherosclerotic burden.

Carotid plaque identified by MRI is associated with cardiovascular events. In the Multi-Ethnic Study of Atherosclerosis (MESA), carotid wall thickness and the presence of a lipid core, as measured by MRI, were predictive of subsequent cardiovascular events beyond traditional risk factors in individuals without a history of cardiovascular disease [26]. Another MESA study found that MRI measurements of wall thickness were more consistently associated with incident coronary heart disease and stroke than IMT measured by ultrasound [27]. Similarly, in the ARIC study, lipid core presence measured by MRI was independently associated with future cardiovascular events after controlling for carotid artery wall thickness [8]. These studies suggest that MRI-based measurements provide high-quality quantification of plaque characteristics and are strong predictors of future cardiovascular risk, offering valuable insight beyond traditional risk factors such as smoking, high blood pressure, high cholesterol, and diabetes. We did not find a significant association between higher ultra-processed food consumption and lipid core presence. Our analysis was restricted to a smaller subset of 553 study participants with a segmental wall thickness $\geq$1.5 mm due to MRI resolution constraints, which may have excluded some cases and limited our statistical power to detect significant associations. Similarly, findings from another study in the Carotid MRI cohort indicated that dietary factors, including carbohydrate and fat intake, glycemic load and index, and Dietary Approaches to Stop Hypertension (DASH) diet score, were not significantly associated with lipid core presence [28]. It is possible that the association between dietary factors and lipid core presence was largely mediated by established vascular risk factors, such as hypertension and diabetes, or that the relationship between diet and lipid core presence was primarily driven by its effect on wall thickness.

Ultra-processed food may contribute to a greater plaque burden due to the unfavorable nutrient profile leading to alterations in blood lipids. In our study, participants who consumed higher levels of ultra-processed foods tended to eat fewer fruits, vegetables, and legumes, had lower fiber intake, and consumed more sugar-sweetened beverages. Viscous fiber, particularly pectin (found in many fruits and vegetables), was inversely associated with IMT progression, which the investigators attributed to the impact of pectin on serum lipid levels [29]. Lipid levels—including total cholesterol, triglycerides, HDL, and LDL cholesterol—are also well-established markers of atherosclerosis [30]. Previous cross-sectional studies have also shown that higher ultra-processed

Table 3
Associations of measures of plaque characteristics with ultra-processed food consumption in either quartiles or servings/day ($n = 768$) [a.]

	Quartile 1 (n = 192)	Quartile 2 (n = 192)	Quartile 3 (n = 192)	Quartile 4 (n = 192)	p-value for trend	Per 1 additional serving of ultra-processed food per day	p-value
Total wall volume based on 8 slices (mm^3)							
Model 1[b]	1 [reference]	0.03 (−0.14, 0.21)	0.03 (−0.17, 0.24)	0.29 (0.08, 0.49)	0.01	0.03 (0.00, 0.05)	0.03
Model 2[c]	1 [reference]	0.10 (−0.07, 0.27)	0.09 (−0.11, 0.28)	0.30 (0.10, 0.51)	0.01	0.03 (0.00, 0.05)	0.03
Model 3[d]	1 [reference]	0.10 (−0.08, 0.27)	0.08 (−0.12, 0.27)	0.28 (0.07, 0.49)	0.02	0.02 (−0.00, 0.05)	0.06
Total lipid core volume over all 8 slices (mm^3)							
Model 1	1 [reference]	0.29 (−0.02, 0.60)	0.38 (−0.19, 0.94)	0.49 (0.14, 0.83)	0.01	0.05 (0.01, 0.10)	0.03
Model 2	1 [reference]	0.34 (−0.01, 0.69)	0.54 (−0.10, 1.17)	0.53 (0.15, 0.92)	0.01	0.06 (0.01, 0.11)	0.02
Model 3	1 [reference]	0.37 (0.01, 0.74)	0.60 (−0.05, 1.26)	0.55 (0.17, 0.92)	0.01	0.06 (0.01, 0.11)	0.03
Maximum segmental wall thickness (mm)							
Model 1	1 [reference]	−0.04 (−0.23, 0.15)	−0.04 (−0.24, 0.16)	0.24 (0.03, 0.46)	0.03	0.02 (−0.00, 0.05)	0.08
Model 2	1 [reference]	0.02 (−0.17, 0.21)	−0.01 (−0.21, 0.19)	0.24 (0.02, 0.45)	0.04	0.02 (−0.01, 0.05)	0.1
Model 3	1 [reference]	0.02 (−0.17, 0.21)	−0.02 (−0.23, 0.19)	0.23 (0.01, 0.45)	0.05	0.02 (−0.01, 0.05)	0.1
Maximum lipid core area of 8 slices (cm^2)							
Model 1	1 [reference]	0.36 (0.04, 0.69)	0.41 (−0.19, 1.00)	0.45 (0.10, 0.79)	0.02	0.05 (−0.01, 0.10)	0.09
Model 2	1 [reference]	0.40 (0.03, 0.78)	0.55 (−0.11, 1.22)	0.47 (0.09, 0.86)	0.03	0.05 (−0.00, 0.10)	0.06
Model 3	1 [reference]	0.40 (0.02, 0.79)	0.61 (−0.07, 1.30)	0.49 (0.12, 0.86)	0.02	0.05 (−0.00, 0.10)	0.06
Lipid core present at any slice on 8 slices[e]							
Model 1	1 [reference]	1.04 (0.71, 1.50)	0.98 (0.66, 1.46)	0.90 (0.62, 1.31)	0.5	0.98 (0.94, 1.03)	0.5
Model 2	1 [reference]	0.98 (0.68, 1.41)	0.93 (0.64, 1.37)	0.86 (0.60, 1.23)	0.4	0.97 (0.93, 1.02)	0.3
Model 3	1 [reference]	0.95 (0.65, 1.37)	0.91 (0.62, 1.33)	0.85 (0.58, 1.24)	0.4	0.97 (0.93, 1.02)	0.3

[a] Coefficients for total wall volume, total lipid core volume, maximum segmental wall thickness, and maximum lipid core area represent the standardized differences in plaque measurements when comparing quartile 4 to quartile 1 of ultra-processed food intake; coefficients for lipid core presence represent the odds ratio for the presence of a lipid core comparing quartile 4 to quartile 1, approximated using Poisson regression with robust standard errors.

[b] Model 1 was the raw model without any covariate adjustment.

[c] Model 2 was adjusted for age, sex, total energy intake, drinking status, smoking status, physical activity score, and education level; For analyses of lipid core presence, the model additionally adjusted for maximum wall thickness.

[d] Model 3 was adjusted for variables in model 2 plus hypertension status, diabetes status and kidney function (two linear spline terms with one knot at 90 mL/min/1.73 m^2).

[e] For analyses of lipid core presence, all models additionally adjusted for maximum wall thickness. The analytical sample size for lipid core presence is 553.

food intake is associated with worse lipid profiles, such as elevated triglyceride levels and lower HDL cholesterol levels, both of which can contribute to atherosclerotic lesions and plaque formation [31,32]. In our analyses, the association between ultra-processed food and carotid plaque persisted even after adjusting for lipid profiles, suggesting that there are other mechanisms through which ultra-processed food impacts carotid plaques.

We also observed higher dietary sodium intake and lower levels of calcium, magnesium, phosphorus, potassium, vitamin A, and vitamin C among participants with higher ultra-processed food consumption. One recent study in the general Swedish population found that urinary sodium excretion was significantly linked to carotid atherosclerosis and coronary stenosis among individuals with normal blood pressure and no history of cardiovascular disease. This finding suggests a potential link between dietary sodium intake and artery damage even before the onset of hypertension [33]. Additionally, micronutrients including vitamins A, C, and E, as well as magnesium, phosphorus, and calcium, are believed to have antioxidant properties that reduce oxidative stress, which can slow atherosclerosis progression [34]. In the ARIC study, vitamin C and alpha-tocopherol (vitamin E) were inversely associated with IMT [35]. Similarly, the Perth Carotid Ultrasound Disease Assessment study found an inverse association between vitamin E and mean IMT in men [36]. In our exploratory analysis, higher consumption of sweet or savory snacks, such as candy bars and syrup, was significantly associated with total lipid core volume and area. While one study in children and adolescents found no association between unhealthy snacks and carotid IMT, it reported an increase in IMT when nuts were replaced with sweet snacks [37]. These findings suggest the need for further investigation into the impact of ultra-processed snacks on carotid plaque characteristics.

Non-nutritional characteristics of ultra-processed foods may also contribute to the progression of atherosclerosis. In the NutriNet-Santé prospective cohort study, various emulsifiers, such as cellulose (E460), carboxymethylcellulose (E466), and monoglycerides and diglycerides of fatty acids (E471 and E472), were associated with higher risk of incident cardiovascular events [38]. Artificial sweeteners, including aspartame, acesulfame K, and saccharin, caused structural changes to apolipoprotein (apo) A-I and HDL, which can lead to cholesterol buildup and cell aging [39].

Neo-formed compounds created during food processing, including acrylamide and advanced glycation end products (AGEs), have been linked to inflammation by increasing the production of reactive oxygen species or altering the function of extracellular matrix molecules in the vessel walls [40,41]. Food packaging materials, such as bisphenol A and phthalates, are associated with carotid plaque and plaque echogenicity, suggesting that these chemicals may have atherogenic properties [42].

Our study has several strengths. To our knowledge, this is the first study to assess associations between ultra-processed food intake and subclinical atherosclerotic plaque characteristics measured by advanced imaging techniques in a relatively large study population. Participant characteristics were well characterized, and the assessment of covariates was thorough and rigorous, allowing for extensive control of potential confounders. The 148-item food frequency questionnaire was extensive and administered in 2004–2005, enabling a more accurate capture of participants' dietary habits that is more reflective of the current food supply than previous dietary assessments. Lastly, the MRI protocol and imaging analysis procedures were standardized across centers, and quality control data were collected and reviewed to ensure reliability.

However, it is important to acknowledge the key limitations of this study. First, due to the cross-sectional design, we are unable to infer temporality or causality, and reverse causation may be present. The

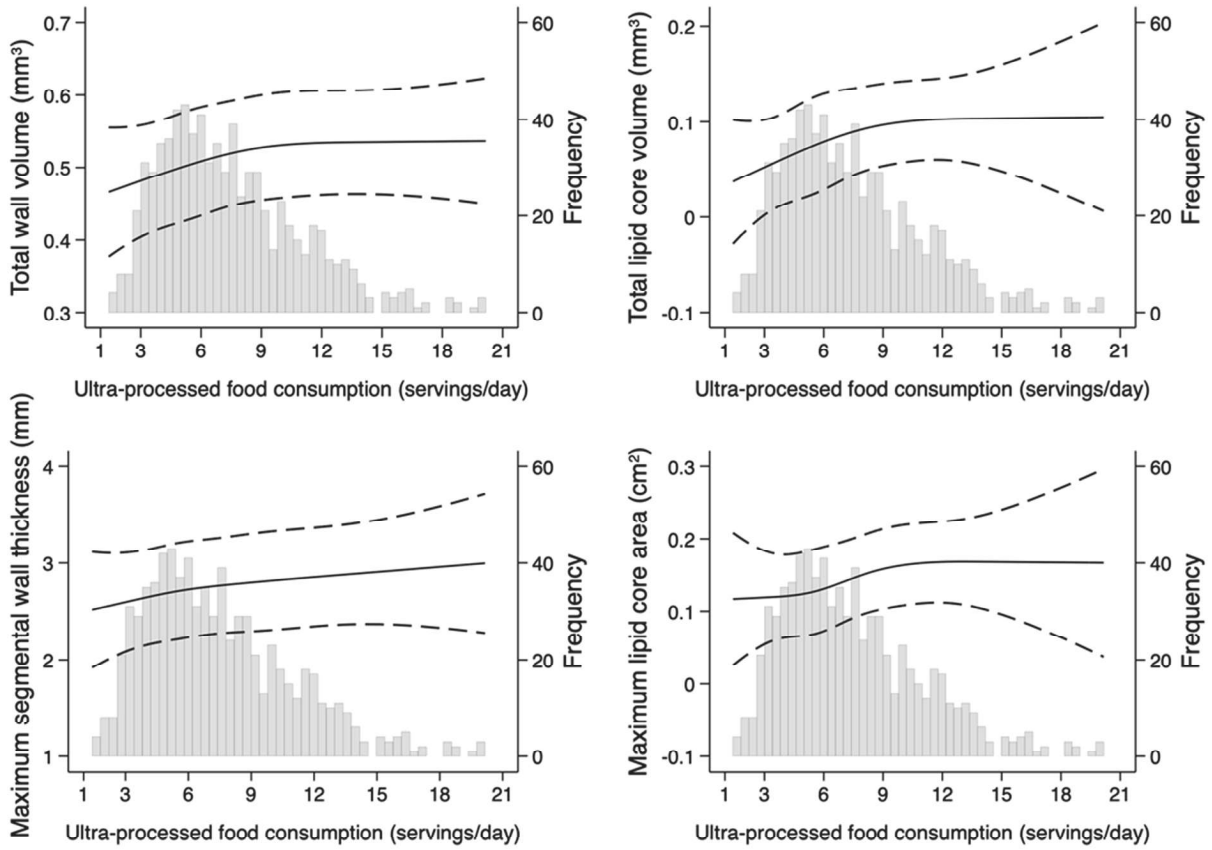


Fig. 3. Associations between measures of plaque characteristics and ultra-processed food consumption in servings per day represented by restricted cubic splines. The model was adjusted for age, sex, total energy intake, drinking status, smoking status, physical activity score, education level, hypertension status, diabetes status and kidney function (two linear spline terms with one knot at 90 mL/min/1.73 m^2). The black solid line represented the changes in plaque characteristics measurements in response to changes in ultra-processed food consumption changes in servings per day. The black dashed lines represent the 95 % CI. The grey histogram represents the frequency of ultra-processed food consumption. The four knots were set at the 5th, 35th, 65th, and 95th percentiles (3.0, 5.5, 8.3, and 13.9 servings per day, respectively).

dietary patterns assessed at one point in time may not reflect individuals' lifelong dietary habits, and it is possible that some participants changed their diets after being diagnosed with certain comorbidities, especially in this older population (age ranges from 60 to 83 years old). Second, dietary intake collected through a food frequency questionnaire is subject to measurement error and recall bias. Since the questionnaire was not specifically designed to capture ultra-processed food intake, misclassification of food items is possible. To address this, two separate coders classified food processing levels, with discrepancies resolved by a third reviewer. However, the lack of details of some of the food items may still be a concern. For example, some fruits and vegetables could not be differentiated as fresh, frozen, or canned, and some canned foods contain added sugar or salt. Items such as hamburgers and fish sandwiches may be classified as fast food, although specific information was not available. Third, we did not have information on calories or grams for each recorded food item, which limited our ability to express ultra-processed food intake as grams per 1000 kcal or as a percentage of total calorie intake. Fourth, our study population consisted only of white participants due to the lack of availability of dietary intake data at all study centers. Whether the findings are generalizable to other racial/ethnic groups requires further investigation. Despite extensively controlling for potential confounders, residual confounding from unmeasured or crudely measured covariates can still be a concern. Lastly, plaque characteristics were assessed only at the largest plaque in the visualized carotid arteries, with the assumption that they are representative of systemic plaque burden [43]. Detection of lipid-rich core in smaller plaques and smaller plaque structures (e.g. fibrous cap thickness) are limited due to resolution constraints of the MRI [11].

In conclusion, our results revealed significant associations between higher ultra-processed food intake and greater atherosclerotic plaque burden, which are key predictors of future cardiovascular events, including stroke and coronary heart disease. Our study suggests potential mechanisms by which ultra-processed food may increase the risk of future cardiovascular disease development. Our study findings contribute to the large and consistent evidence on the harmful cardiovascular consequences of ultra-processed food consumption in the U.S.

List of supplemental material

Figs. S1 and S2

Tables S1 and S2

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CRediT authorship contribution statement

Shutong Du: Writing – original draft, Formal analysis. **Valerie K. Sullivan:** Writing – review & editing. **Kunihiro Matsushita:** Writing – review & editing. **Seamus P. Whelton:** Writing – review & editing. **Lyn M. Steffen:** Writing – review & editing. **Michael Fang:** Writing – review & editing. **Lawrence J. Appel:** Writing – review & editing. **Bruce A. Wasserman:** Writing – review & editing. **Casey M. Rebholz:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Casey Rebholz reports financial support was provided by National Heart Lung and Blood Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.101065.

Data availability

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

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