RESEARCH ARTICLE

# Associations Between Ultra-Processed Food Consumption and Adverse Brain Health Outcomes

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## Abstract

### Background and Objectives

Ultra-processed foods (UPFs) are linked to cardiometabolic diseases and neurologic outcomes, such as cognitive decline and stroke. However, it is unclear whether food processing confers neurologic risk independent of dietary pattern information. We aimed to (1) investigate associations between UPFs and incident cognitive impairment and stroke and (2) compare these associations with other commonly recommended dietary patterns in the REasons for Geographic and Racial Differences in Stroke study. This prospective, observational cohort study enrolled Black and White adults in the United States from 2003 to 2007.

### Methods

The NOVA system was used to categorize items from a baseline food frequency questionnaire according to the level of processing. Participants with incomplete or implausible self-reported dietary data were excluded. Consumption for each category (grams) was normalized to total grams consumed. Scores quantifying adherence to a Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet were also calculated. Incident cognitive impairment was defined using performance relative to a normative sample on memory and fluency assessments. Incident stroke was identified through adjudicated review of medical records.

### Results

The cognitive impairment cohort (n = 14,175) included participants without evidence of impairment at baseline who underwent follow-up testing. The stroke cohort (n = 20,243) included participants without a history of stroke. In multivariable Cox proportional hazards models, a 10% increase in relative intake of UPFs was associated with higher risk of cognitive impairment (hazard ratio [HR] = 1.16, 95% CI 1.09–1.24, $p = 1.01 \times 10^{-5}$) and intake of unprocessed or minimally processed foods with lower risk of cognitive impairment (HR = 0.88, 95% CI 0.83–0.94, $p = 1.83 \times 10^{-4}$). Greater intake of UPFs (HR = 1.08, 95% CI 1.02–1.14, $p = 1.12 \times 10^{-2}$) and unprocessed or minimally processed foods (HR = 0.91, 95% CI 0.86–0.95, $p = 2.13 \times 10^{-4}$) were also associated with risk of stroke in multivariable Cox models. The effect of UPFs on stroke risk was greater among Black than White participants (UPF-by-race interaction HR = 1.15, 95% CI 1.03–1.29, $p = 1.50 \times 10^{-2}$). Associations between UPFs and both cognitive impairment and stroke were independent of adherence to the Mediterranean, DASH, and MIND diets.

### Discussion

Food processing may be important to brain health in older adults independent of known risk factors and adherence to recommended dietary patterns.

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## Glossary

**BMI** = body mass index; **CESD-4** = four-item Center for Epidemiologic Studies Depression Scale; **DASH** = Dietary Approaches to Stop Hypertension; **FFQ** = food frequency questionnaire; **HR** = hazard ratio; **MIND** = Mediterranean-DASH Intervention for Neurodegenerative Delay; **REGARDS** = REasons for Geographic and Racial Differences in Stroke; **UPFs** = ultra-processed foods.

## Introduction

Stroke and dementia are the 2 leading neurologic causes of morbidity and mortality in older adults.[1] Diet is a modifiable risk factor of both stroke and cognitive impairment, and greater adherence to specific dietary patterns, such as a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diet, has been associated with a reduced risk of stroke and attenuated cognitive decline.[2-8] Another dietary pattern derived from the Mediterranean and DASH diets, the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, has also been linked to slowed age-related cognitive decline and risk of incident dementia.[9-11]

A shift in prepared foods in recent decades has been the increased production of ultra-processed foods (UPFs).[12] UPFs are defined by the presence of processed food substances never or rarely used in kitchens and additives designed to make final products more palatable or appealing.[12] Although the majority of caloric intake by consumers in the United States is derived from UPFs,[13] consumption of UPFs has been associated with increased risk of cardiovascular disease, obesity, and metabolic syndrome in cross-sectional and prospective cohort studies.[14]

Several studies have also observed associations between UPF intake and adverse neurologic outcomes. For example, greater UPF consumption has been associated with higher risk of incident stroke in the French NutriNet-Santé cohort.[15] Other cohort studies have found associations between UPF intake and accelerated cognitive decline.[16,17] However, it remains controversial whether the degree of food processing confers a risk of adverse neurologic outcomes that is independent of the nutritional profile of individual food items and groups.

In this study, we explored associations between UPFs and risk of incident stroke and cognitive impairment in the REasons for Geographic and Racial Differences in Stroke (REGARDS) project, a longitudinal study of Black and White adults in the United States aimed at assessing the causes of stroke.[18] Our findings underscore the role of food processing in overall brain health and highlight associations between differentially processed foods and neurologic outcomes that are independent of adherence to other recommended dietary patterns.

## Methods

### Study Population

The REGARDS study is an ongoing prospective cohort study that enrolled non-Hispanic Black and White adults aged 45 years or older from 2003 to 2007. The methods and study design have been described in detail elsewhere.[18,19] Consented participants provided clinical, demographic, and lifestyle information over the phone at the time of entry into the study. Exclusion criteria included medical conditions that would prevent long-term study participation, a history of malignancy or active cancer treatment, living in a nursing home, inability to communicate in English, and a self-reported race apart from Black or White. Associations between dietary scores and incident stroke and cognitive impairment were analyzed in separate subcohorts of the REGARDS study. The stroke cohort included participants without a history of stroke at baseline. The cognitive impairment cohort included participants who did not have evidence of impairment at baseline and had sufficient cognitive testing data available at one or more follow-up time points.

### Neurologic Outcomes

Standardized questionnaires were administered during every 6-month telephone interview to assess for stroke symptoms, hospitalizations, and ambulatory evaluations for stroke or transient ischemic attack. If one of these events was reported, a participant's medical records were reviewed by at least 2 physicians, including a neurologist. Participants were deemed to have a stroke if they experienced focal neurologic deficit(s) lasting ≥24 hours[20] or had nonfocal deficit(s) and neuroimaging findings consistent with acute ischemic or hemorrhagic stroke.

The operationalization of incident cognitive impairment in the REGARDS study has been described elsewhere.[21,22] Impairment was defined using 2 memory assessments (Word List Learning and Delayed Recall) and 2 fluency assessments (Animal Fluency and Letter F Fluency).[21,22] A normative sample of participants (n = 6,264) without conditions associated with cognitive performance was selected from the pool of participants who completed a second in-home interview. Participants were excluded from the normative sample if they had a history of stroke; a Medicare (ICD-10) or self-reported dementia diagnosis; dementia-like symptoms, based on the AD8 Dementia Screening Interview[23]; significant depressive symptoms, based on the four-item Center for Epidemiologic Studies Depression Scale (CESD-4)[24]; a history of head injury with loss of consciousness; or a designated health care surrogate.

Baseline cognitive assessments from the normative sample were used to obtain predicted scores and standard deviations for all cognitive assessments, which were used to infer impairment

across the entire cohort. Predicted scores were calculated in the normative sample using separate linear regressions for each cognitive assessment. Regression models included age at the time of assessment, race, sex, education level, and all significant pairwise interactions between these covariates.

Participants were considered impaired on a specific assessment if their scores were 1.5 standard deviations below their predicted scores. Cognitive impairment was defined as impairment on ≥1 memory assessment and ≥1 fluency assessment. All 4 assessments had to be administered and scored on the same follow-up call for impairment to be assigned. Cognitive impairment was considered incident if participants were free from impairment at baseline. Participants were considered impaired at baseline if they scored ≤4 on a baseline Six-Item Screener, a brief and previously validated test derived from the full Mini-Mental State Examination.[25] Participants meeting the criteria for impairment during a single follow-up call were censored at that time.

## Covariates

Participants' age, race, and sex were determined from self-report. Clinical variables in regression models for stroke included current smoking status, hypertension, diabetes mellitus, cardiovascular disease, left ventricular hypertrophy, and atrial fibrillation. Smoking status was determined by self-report. During an in-home visit, blood pressure was measured twice, and the average of 2 measurements was used. Hypertension was defined as (1) a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or (2) the self-reported use of antihypertensive medications. Diabetes mellitus was defined as (1) the current use of diabetes medications (e.g., insulin, oral glucose-lowering agents) or (2) a blood glucose concentration of ≥126 mg/dL (fasted) or ≥200 mg/dL (non-fasted). Cardiovascular disease was defined as (1) a self-reported history of myocardial infarction or coronary revascularization or (2) evidence of a prior myocardial infarction on a baseline ECG. Left ventricular hypertrophy was diagnosed based on review of the baseline ECG. Atrial fibrillation was determined from self-reported history or the presence of atrial fibrillation on the baseline ECG.

Additional covariates in regression models for cognitive impairment included educational attainment, annual income, physical activity, body mass index (BMI) category, alcohol use, and depressive symptoms. Participants were classified based on BMI as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30). Highest level of education (less than high school, high school graduate, some college, or college graduate), annual income (≤$20 K, $20–34 K, $35–74 K, or ≥$75 K), and frequency of moderate or vigorous physical activity (none, 1–3 times/wk, or ≥4 times/wk) were each determined from self-report. National Institute on Alcohol Abuse and Alcoholism categories were used to classify alcohol consumption (heavy, moderate, or none) based on the number of self-reported drinks per week. Depressive symptoms were quantified using the CESD-4; significant depressive symptoms were defined as a CESD-4 ≥4.

## Dietary Indices

The NOVA classification system[12] was used to categorize food and drink items from a baseline Block 1998 Food Frequency Questionnaire (FFQ)[26] according to the level of processing (eTable 1) as previously reported.[27] Categories included NOVA1 (unprocessed or minimally processed foods), NOVA2 (processed culinary ingredients), NOVA3 (processed foods), and NOVA4 (ultra-processed foods). Daily intake in grams for each NOVA category was normalized to total grams consumed. Our primary analyses were based on a weight ratio to account for processed foods with few or no calories (e.g., artificially sweetened beverages) and non-nutritional factors related to food processing (e.g., additives, neoformed contaminants, or structural alterations to raw foods).[15] However, additional sensitivity analyses were performed using an energy ratio (% of total calories consumed). Calorie information available from the US Department of Agriculture Food Composition Database was used to estimate the calories per gram for FFQ items.[28]

Scores quantifying adherence to Mediterranean, DASH, and MIND dietary patterns were also obtained from FFQ data as previously described.[2,9,29] Mediterranean diet scores (range: 0–9) reflected intake of vegetables, fruits, legumes, cereals, fish, monounsaturated lipids, dairy products, meat products, and alcohol.[2] DASH diet scores (range: 8–40) were derived from intake of fruits, vegetables, whole grains, nuts/legumes, low-fat dairy products, red and processed meats, sweetened beverages, and sodium.[29] MIND diet scores (range: 0–15) were based on similar food groups as Mediterranean and DASH scores (i.e., leafy greens and other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, wine, red meats, margarine, cheese, pastries/sweets, fried/fast food). However, the MIND score was originally developed to emphasize foods associated with incident dementia and cognitive decline.[9] Subjects with missing, incomplete, or biologically implausible FFQ results were excluded as described elsewhere.[26]

## Statistical Analyses

All statistical analyses were performed in R (R Project for Statistical Computing) version 4.2. To account for missing dietary data, we chose to use listwise deletion; missingness in categorical covariates was modeled explicitly by creating another variable factor level (i.e., "unknown") to account for observations that were potentially not missing at random.

Cox proportional hazards models were used to evaluate associations between dietary variables and incident stroke or cognitive impairment. A base model for each outcome included demographic covariates. The stroke base model included age, race, and sex. The base model also included an age-by-race interaction term because of the presence of this interaction in previous REGARDS studies.[30] The cognitive impairment base model included age, race, sex, income, and education level.[17] A fully adjusted model for stroke also included current smoking status, atrial fibrillation, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular hypertrophy.[31] The

fully adjusted model for cognitive impairment included physical activity, BMI category, hypertension, diabetes mellitus, cardiovascular disease, smoking status, alcohol consumption, and depressive symptoms.[17] Total daily caloric intake was also included as a covariate in all Cox models.

As a sensitivity analysis, Z-scored performance on each cognitive assessment as a function of dietary intake was further assessed using linear mixed-effects models[17,32] with random slopes and intercepts. These models included the covariates listed above, along with (1) an age-by-diet interaction to estimate the effect of diet on the rate of change in cognitive performance with increasing age and (2) the number of prior cognitive assessments to account for possible retesting effects.

To determine whether incorporating an additional dietary index added significant predictive value to Cox proportional hazards models that already included one dietary index, the partial log-likelihoods of the 2 nested models were compared using the likelihood ratio test. Nested Cox models were each implemented on the same subset of participants who did not have missing data for either diet scores or other covariates. All other *p*-values from Cox regression models were obtained using Wald tests.

### Standard Protocol Approvals, Registrations, and Patient Consents

The REGARDS study was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all participants.

### Data Availability

Deidentified REGARDS study are available to qualified researchers upon approval of a research proposal and data use agreement. Additional details are available at regardsstudy.org.

## Results

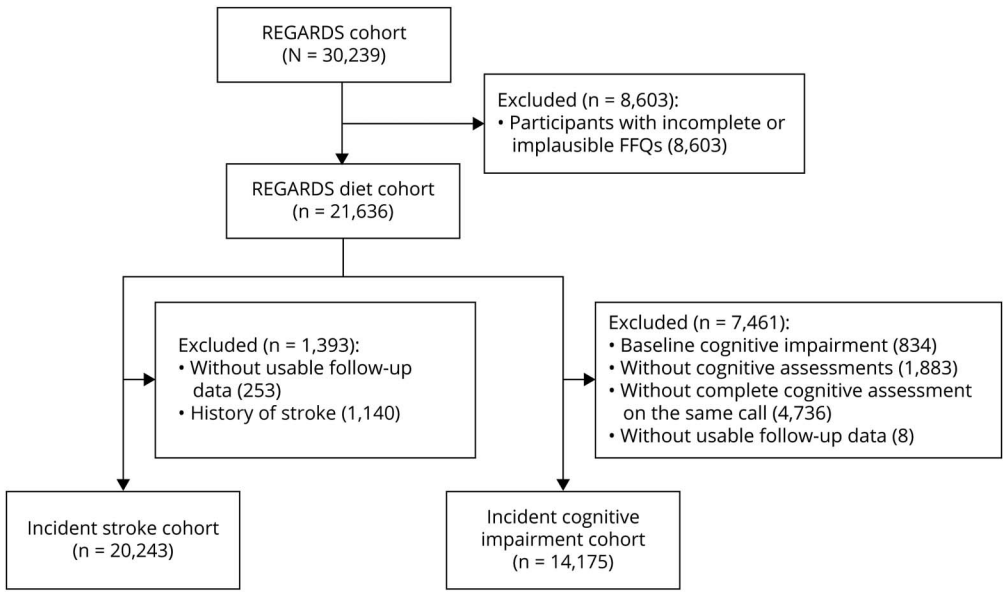
### Study Population

The REGARDS study enrolled 30,239 community-dwelling participants from 2003 to 2007, and 21,636 participants had reliable self-reported dietary data at baseline. The stroke cohort (n = 20,243) included participants with no history of stroke at baseline and who had follow-up data available. The cognitive impairment cohort (n = 14,175) included participants who did not have evidence of impairment at baseline, underwent follow-up cognitive testing, and had sufficient cognitive testing data available at one or more time points (Figure 1). Incident stroke cases were adjudicated through September 30, 2020, and incident cognitive impairment cases through September 30, 2021. Baseline characteristics of participants in the stroke and cognitive impairment cohorts are presented in Table 1. In the stroke and cognitive impairment cohorts, consumption of UPFs (NOVA4) was negatively correlated with adherence to the Mediterranean, DASH, and MIND diets. By contrast, consumption of unprocessed or minimally processed foods (NOVA1) and processed foods (NOVA3) was positively correlated with Mediterranean, DASH, and MIND diet scores (eTable 2).

### Incident Stroke

We compared the risk of stroke associated with intake across NOVA categories to the risk associated with adherence to

**Figure 1** Participant Flow Diagram




Participants in a subgroup of the REasons for Geographic and Racial Differences in Stroke (REGARDS) study with self-reported dietary data were divided into separate cohorts to assess incident stroke and cognitive impairment. FFQ = Food Frequency Questionnaire.

**Table 1** Baseline Characteristics of the Study Cohort

| Outcome | Covariate | Event-free participants | Incident cases | *p* Value |
|---|---|---|---|---|
| **Stroke** | Number of participants | 19,135 | 1,108 | — |
| | Mean follow-up time (y) ± SD | 11.2 ± 4.7 | 6.5 ± 4.1 | — |
| | Mean age, y ± SD | 64.4 ± 9.2 (n = 19,135) | 69.2 ± 8.7 (n = 1,108) | $9.03 \times 10^{-62}$ |
| | Female sex | 56.5% (n = 19,135) | 50.5% (n = 1,108) | $1.12 \times 10^{-4}$ |
| | Black race | 32.9% (n = 19,135) | 33.3% (n = 1,108) | 0.818 |
| | Current smoker | 13.4% (n = 19,060) | 13.8% (n = 1,105) | 0.872 |
| | Hypertension | 70.7% (n = 19,092) | 82.8% (n = 1,104) | $1.00 \times 10^{-18}$ |
| | Diabetes mellitus | 17.8% (n = 18,495) | 25.7% (n = 1,079) | $1.23 \times 10^{-9}$ |
| | Cardiovascular disease | 15.9% (n = 18,825) | 24.8% (n = 1,093) | $1.03 \times 10^{-12}$ |
| | Left ventricular hypertrophy | 8.4% (n = 18,858) | 13.1% (n = 1,098) | $8.82 \times 10^{-7}$ |
| | Atrial fibrillation | 8.0% (n = 18,756) | 13.2% (n = 1,088) | $9.10 \times 10^{-8}$ |
| | Proportion of diet (grams/d) ± SD | n = 16,084 | n = 953 | — |
| | NOVA1 | 66.5 ± 14.9% | 65.9 ± 14.9% | |
| | NOVA2 | 0.5 ± 0.6% | 0.5 ± 0.6% | |
| | NOVA3 | 7.9 ± 8.2% | 8.3 ± 8.7% | |
| | NOVA4 | 25.1 ± 13.9% | 25.4 ± 14.2% | |
| | Proportion of diet (calories/day) ± SD | n = 19,135 | n = 1,108 | — |
| | NOVA1 | 35.9 ± 10.9% | 36.1 ± 11.2% | |
| | NOVA2 | 3.6 ± 3.5% | 3.5 ± 3.4% | |
| | NOVA3 | 12.4 ± 8.9% | 12.7 ± 9.1% | |
| | NOVA4 | 48.1 ± 12.2% | 47.7 ± 12.1% | |
| | Median Mediterranean diet score, IQR | 4, 3 (n = 18,804) | 4, 3 (n = 1,087) | — |
| | Median DASH diet score, IQR | 24, 6 (n = 19,135) | 24, 6 (n = 1,108) | — |
| | Median MIND diet score, IQR | 7.0, 2.5 (n = 19,135) | 7.0, 2.5 (n = 1,108) | — |
| **Cognitive impairment** | Number of participants | 13,407 | 768 | — |
| | Mean follow-up time (y) ± SD | 10.9 ± 4.1 | 7.5 ± 3.6 | — |
| | Mean age, y ± SD | 63.4 ± 8.6 (n = 13,407) | 65.8 ± 8.8 (n = 768) | $1.18 \times 10^{-12}$ |
| | Female sex | 57.9% (n = 13,407) | 59.6% (n = 768) | 0.367 |
| | Black race | 30.9% (n = 13,407) | 24.3% (n = 768) | $1.08 \times 10^{-4}$ |
| | Educational attainment | n = 13,406 | n = 768 | $1.23 \times 10^{-3}$ |
| | Less than high school | 6.7% | 5.1% | |
| | High school graduate | 24.5% | 20.3% | |
| | Some college | 27.3% | 26.0% | |
| | College graduate | 41.5% | 48.6% | |
| | Annual income | n = 11,935 | n = 681 | $5.00 \times 10^{-4}$ |
| | <$20 K | 13.5% | 20.0% | |
| | $20–34 K | 24.9% | 28.8% | |
| | $35–74 K | 38.2% | 38.0% | |

Continued

**Table 1** Baseline Characteristics of the Study Cohort *(continued)*

| Outcome | Covariate | Event-free participants | Incident cases | *p* Value |
|---|---|---|---|---|
| | >$75 K | 23.4% | 13.2% | |
| | Physical activity | n = 13,266 | n = 765 | $4.51 \times 10^{-2}$ |
| | None | 29.8% | 32.9% | |
| | 1–3 times/wk | 39.4% | 39.5% | |
| | ≥4 times/wk | 30.8% | 27.6% | |
| | BMI category | n = 13,343 | n = 763 | 0.871 |
| | Underweight (<18.5) | 0.9% | 0.9% | |
| | Normal weight (18.5–24.9) | 24.3% | 24.0% | |
| | Overweight (25.0–29.9) | 38.1% | 39.3% | |
| | Obese (≥30) | 36.6% | 35.8% | |
| | Current smoker | 11.7% (n = 13,362) | 15.6% (n = 763) | $1.91 \times 10^{-3}$ |
| | Hypertension | 69.6% (n = 13,382) | 74.4% (n = 765) | $6.19 \times 10^{-3}$ |
| | Diabetes mellitus | 15.6% (n = 13,003) | 23.1% (n = 741) | $1.04 \times 10^{-6}$ |
| | Cardiovascular disease | 14.2% (n = 13,199) | 17.7% (n = 755) | $2.46 \times 10^{-2}$ |
| | Depressive symptoms (CESD-4 ≥4) | 7.9% (n = 13,309) | 13.1% (n = 765) | $7.35 \times 10^{-6}$ |
| | Alcohol use (NIAAA categories) | n = 13,206 | n = 760 | $3.47 \times 10^{-5}$ |
| | None | 56.6% | 65.1% | |
| | Moderate | 38.9% | 30.8% | |
| | Heavy | 4.5% | 4.1% | |
| | Proportion of diet (grams/d) ± SD | n = 11,034 | n = 646 | — |
| | NOVA1 | 66.8 ± 14.5% | 66.8 ± 14.8% | |
| | NOVA2 | 0.5 ± 0.6% | 0.5 ± 0.6% | |
| | NOVA3 | 8.0 ± 8.1% | 6.9 ± 6.8% | |
| | NOVA4 | 24.6 ± 13.7% | 25.8 ± 14.2% | |
| | Proportion of diet (calories/day) ± SD | n = 13,407 | n = 768 | — |
| | NOVA1 | 35.7 ± 10.8% | 35.8 ± 11.0% | |
| | NOVA2 | 3.7 ± 3.5% | 3.5 ± 3.6% | |
| | NOVA3 | 12.8 ± 8.9% | 11.9 ± 8.4% | |
| | NOVA4 | 47.8 ± 12.1% | 48.8 ± 12.0% | |
| | Median Mediterranean diet score, IQR | 4, 3 (n = 13,206) | 4, 2 (n = 760) | — |
| | Median DASH diet score, IQR | 24, 6 (n = 13,407) | 24, 6 (n = 768) | — |
| | Median MIND diet score, IQR | 7.0, 2.5 (n = 13,407) | 7, 3 (n = 768) | — |

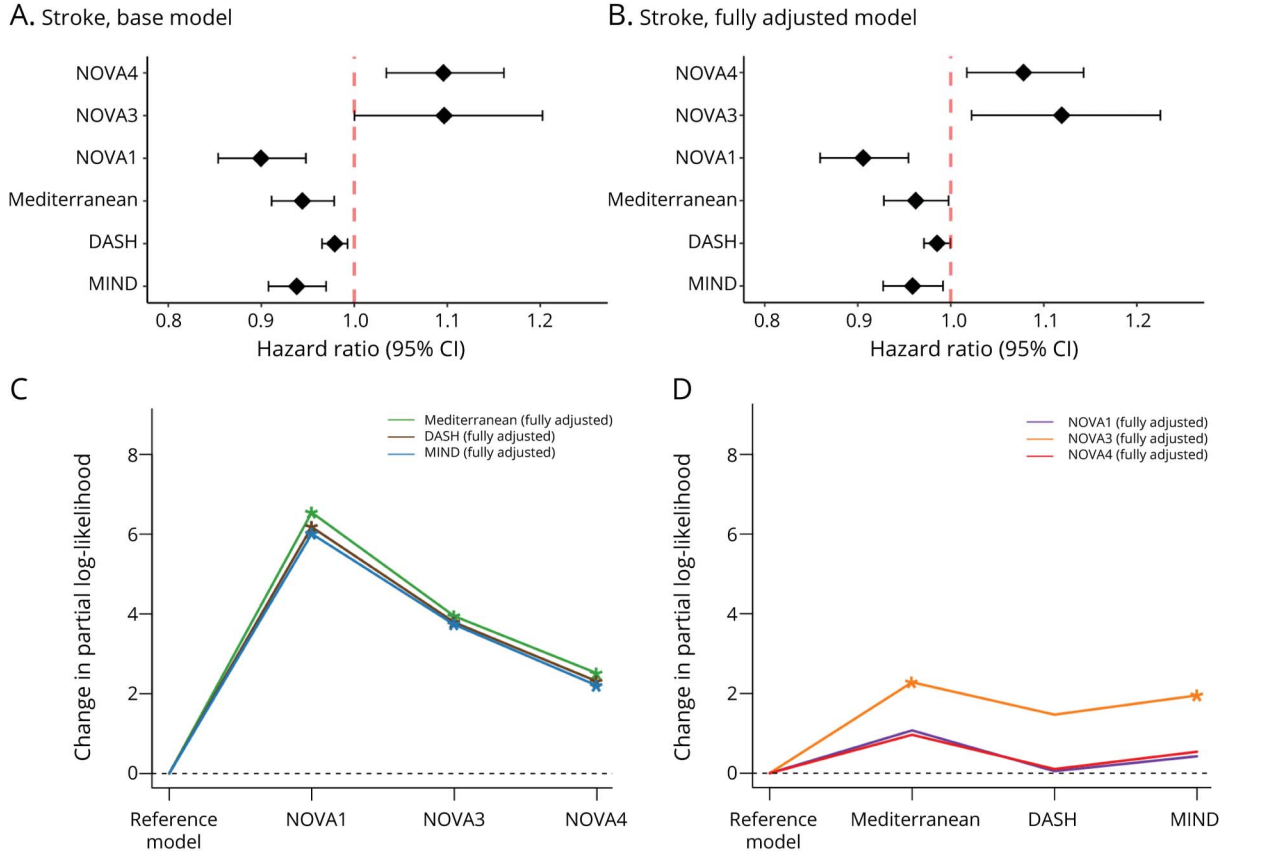
Abbreviations: BMI = body mass index; CESD-4 = Center for Epidemiologic Studies Depression Scale; DASH = Dietary Approaches to Stop Hypertension; IQR = interquartile range; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay; NIAAA = National Institute on Alcohol Abuse and Alcoholism.
Demographic and clinical characteristics are shown separately for the incident stroke and cognitive impairment cohorts. *p*-Values were calculated using two-sample *t* tests or Fisher exact tests as indicated. The total number of participants with data available for each variable is indicated in parentheses.

other diet patterns, including the Mediterranean, DASH, and MIND diets.

Greater consumption of UPFs was associated with increased risk of incident stroke (hazard ratio [HR] per 10% increase in proportion consumed = 1.10, 95% CI 1.03–1.16, $p = 1.87 \times 10^{-3}$) in Cox proportional hazards models adjusted for age, race, sex, age-by-race interaction, and total daily caloric intake (base model). A similar effect (HR = 1.10, 95% CI 1.00–1.20, $p = 4.95 \times 10^{-2}$) was observed with NOVA3 intake while consumption of NOVA1 items was associated with reduced stroke risk (HR = 0.90, 95% CI 0.85–0.95, $p = 7.47 \times 10^{-5}$) (Figure 2A). After further adjustment for smoking status, atrial fibrillation, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular hypertrophy (fully adjusted model), NOVA4 intake (HR = 1.08, 95% CI 1.02–1.14, $p = 1.12 \times 10^{-2}$) and NOVA3 intake (HR = 1.12, 95% CI 1.02–1.23, $p = 1.47 \times 10^{-2}$) remained associated with higher stroke risk while NOVA1 consumption remained associated with lower stroke risk (HR = 0.91, 95% CI 0.86–0.95, $p = 2.13 \times 10^{-4}$) (Figure 2B). Intake of processed culinary ingredients (NOVA2) was not associated with stroke risk in either the base or fully adjusted model (eTable 3). The effect of NOVA4 intake on stroke risk was greater among Black participants, with significant effect modification in the base model (HR of Black vs White race interaction = 1.13, 95% CI 1.01–1.27, $p = 2.71 \times 10^{-2}$) and fully adjusted model (HR = 1.15, 95% CI 1.03–1.29, $p = 1.50 \times 10^{-2}$) (eTable 3).

Greater adherence to a Mediterranean diet (HR per 1-point = 0.94, 95% CI 0.91–0.98, $p = 1.58 \times 10^{-3}$), DASH diet (HR = 0.98, 95% CI 0.97–0.99, $p = 2.94 \times 10^{-3}$), and MIND diet (HR = 0.94, 95% CI 0.91–0.97, $p = 1.51 \times 10^{-4}$) was also associated with decreased risk of stroke in the base model (Figure 2A). The Mediterranean (HR = 0.96, 95% CI 0.93–1.00, $p = 3.72 \times 10^{-2}$), DASH (HR = 0.99, 95% CI 0.97–1.00, $p = 4.32 \times 10^{-2}$), and MIND (HR = 0.96, 95% CI 0.93–0.99, $p = 1.44 \times 10^{-2}$) diets remained associated with

**Figure 2** Association Between Ultra-Processed Food Intake and Incident Stroke




(A and B) Forest plots demonstrating hazard ratios (HR) and 95% confidence intervals (CI) for stroke risk associated with intake of NOVA1 (unprocessed or minimally processed), NOVA3 (processed), and NOVA4 (ultra-processed) items, along with higher Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet scores. HRs for NOVA categories represent the HR per 10% relative increase in consumption (in % grams/d). HRs for other dietary patterns represent the HR per 1-point increase in score. Forest plots are shown for (A) a base model, adjusted for age, race, sex, total caloric intake, and age-by-race interaction and (B) a fully adjusted model, which also included smoking status, atrial fibrillation, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular hypertrophy. (C) Change in partial log-likelihood associated with adding NOVA1, NOVA3, or NOVA4 intake to reference Cox models that included adherence to a Mediterranean, DASH, or MIND diet and covariates from the fully adjusted model. Points labeled with an asterisk (*) represent significant ($p < 0.05$) changes from the reference model partial log-likelihood. (D) Change in partial log-likelihood associated with adding adherence to a Mediterranean, DASH, or MIND diet to reference Cox models that included NOVA1, NOVA3, or NOVA4 intake and covariates from the fully adjusted model.

**Table 2** Associations Between Dietary Indices and Incident Stroke After Adjustment for Other Dietary Indices

| | | Base model | | Fully adjusted model | |
|---|---|---|---|---|---|
| **Dietary index of interest** | **Dietary index (adjusted for)** | **HR (95% CI)** | ***p* Value** | **HR (95% CI)** | ***p* Value** |
| **NOVA1** | Mediterranean | 0.90 (0.85–0.95) | $1.25 \times 10^{-4}$ | 0.90 (0.86–0.95) | $2.16 \times 10^{-4}$ |
| **NOVA3** | Mediterranean | 1.13 (1.03–1.23) | $9.87 \times 10^{-3}$ | 1.14 (1.05–1.25) | $3.45 \times 10^{-3}$ |
| **NOVA4** | Mediterranean | 1.08 (1.02–1.15) | $8.28 \times 10^{-3}$ | 1.07 (1.01–1.14) | $2.26 \times 10^{-2}$ |
| **Mediterranean** | NOVA1 | 0.95 (0.92–0.99) | $1.70 \times 10^{-2}$ | 0.97 (0.93–1.01) | 0.143 |
| **Mediterranean** | NOVA3 | 0.94 (0.91–0.98) | $2.14 \times 10^{-3}$ | 0.96 (0.92–1.00) | $3.27 \times 10^{-2}$ |
| **Mediterranean** | NOVA4 | 0.96 (0.92–0.99) | $2.29 \times 10^{-2}$ | 0.97 (0.93–1.01) | 0.165 |
| **NOVA1** | DASH | 0.90 (0.85–0.95) | $3.38 \times 10^{-4}$ | 0.90 (0.85–0.95) | $3.31 \times 10^{-4}$ |
| **NOVA3** | DASH | 1.12 (1.03–1.23) | $1.22 \times 10^{-2}$ | 1.14 (1.04–1.25) | $4.19 \times 10^{-3}$ |
| **NOVA4** | DASH | 1.08 (1.01–1.15) | $1.61 \times 10^{-2}$ | 1.07 (1.01–1.15) | $2.90 \times 10^{-2}$ |
| **DASH** | NOVA1 | 0.99 (0.98–1.01) | 0.281 | 1.00 (0.98–1.01) | 0.748 |
| **DASH** | NOVA3 | 0.98 (0.97–1.00) | $1.23 \times 10^{-2}$ | 0.99 (0.97–1.00) | $8.69 \times 10^{-2}$ |
| **DASH** | NOVA4 | 0.99 (0.97–1.01) | 0.263 | 1.00 (0.98–1.01) | 0.649 |
| **NOVA1** | MIND | 0.91 (0.86–0.96) | $4.50 \times 10^{-4}$ | 0.91 (0.86–0.96) | $3.99 \times 10^{-4}$ |
| **NOVA3** | MIND | 1.12 (1.03–1.23) | $1.26 \times 10^{-2}$ | 1.14 (1.04–1.25) | $4.52 \times 10^{-3}$ |
| **NOVA4** | MIND | 1.08 (1.01–1.14) | $2.06 \times 10^{-2}$ | 1.07 (1.01–1.14) | $3.29 \times 10^{-2}$ |
| **MIND** | NOVA1 | 0.96 (0.93–1.00) | $4.74 \times 10^{-2}$ | 0.98 (0.95–1.02) | 0.357 |
| **MIND** | NOVA3 | 0.94 (0.91–0.98) | $2.07 \times 10^{-3}$ | 0.96 (0.93–1.00) | $4.85 \times 10^{-2}$ |
| **MIND** | NOVA4 | 0.96 (0.93–1.00) | $4.23 \times 10^{-2}$ | 0.98 (0.94–1.02) | 0.300 |

Abbreviations: CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.
Hazard ratios (HRs) for the dietary index in the first column are shown after adjustment for the dietary index indicated in the second column. NOVA1, NOVA3, and NOVA4 intake were compared with other healthy dietary patterns given the associations between these NOVA categories and stroke. Multivariable Cox proportional hazards models were adjusted for age, race, sex, total caloric intake, and age-by-race interaction (base model) and further adjusted for smoking status, atrial fibrillation, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular hypertrophy (fully adjusted model).

reduced stroke risk in the fully adjusted model (Figure 2B). The effect of the DASH diet was magnified among Black participants (HR of interaction, base model = 0.97, 95% CI 0.94–1.00, $p = 2.70 \times 10^{-2}$; HR, fully adjusted model = 0.96, 95% CI 0.94–0.99, $p = 2.01 \times 10^{-2}$) (eTable 3).

We explored whether alterations in stroke risk associated with food processing were independent of other dietary scores. The fit (partial log-likelihood) of models that included one dietary index was compared with the fit of models that incorporated an additional dietary index. In the base model, adding intake of NOVA1 or NOVA4 items to models that included Mediterranean, DASH, or MIND diet scores resulted in increased partial log-likelihood (eTable 4). Consistent with these results, intake of NOVA1 and NOVA4 items was independently associated with stroke after adjustment for adherence to a Mediterranean, DASH, or MIND diet. The Mediterranean and MIND diets, but not the DASH diet, were associated with stroke after adjustment for NOVA1 or NOVA4 intake (Table 2).

In the fully adjusted model, adding NOVA1 or NOVA4 intake to models that included the Mediterranean, DASH, or MIND diets resulted in increased partial log-likelihood (Figure 2C). By contrast, adding other dietary patterns to fully adjusted models that included NOVA1 or NOVA4 intake did not result in significantly increased partial log-likelihood (Figure 2D, eTable 4). Consistent with these findings, associations between NOVA1 or NOVA4 intake and stroke risk persisted in fully adjusted models that included adherence to a Mediterranean, DASH, or MIND diet. However, associations between the Mediterranean, DASH, and MIND dietary patterns and stroke were not significant after adjustment for NOVA1 or NOVA4 intake (Table 2). Notably, there were no significant interactions between NOVA1 or NOVA4 consumption and the Mediterranean, DASH, or MIND dietary patterns (eTable 5).

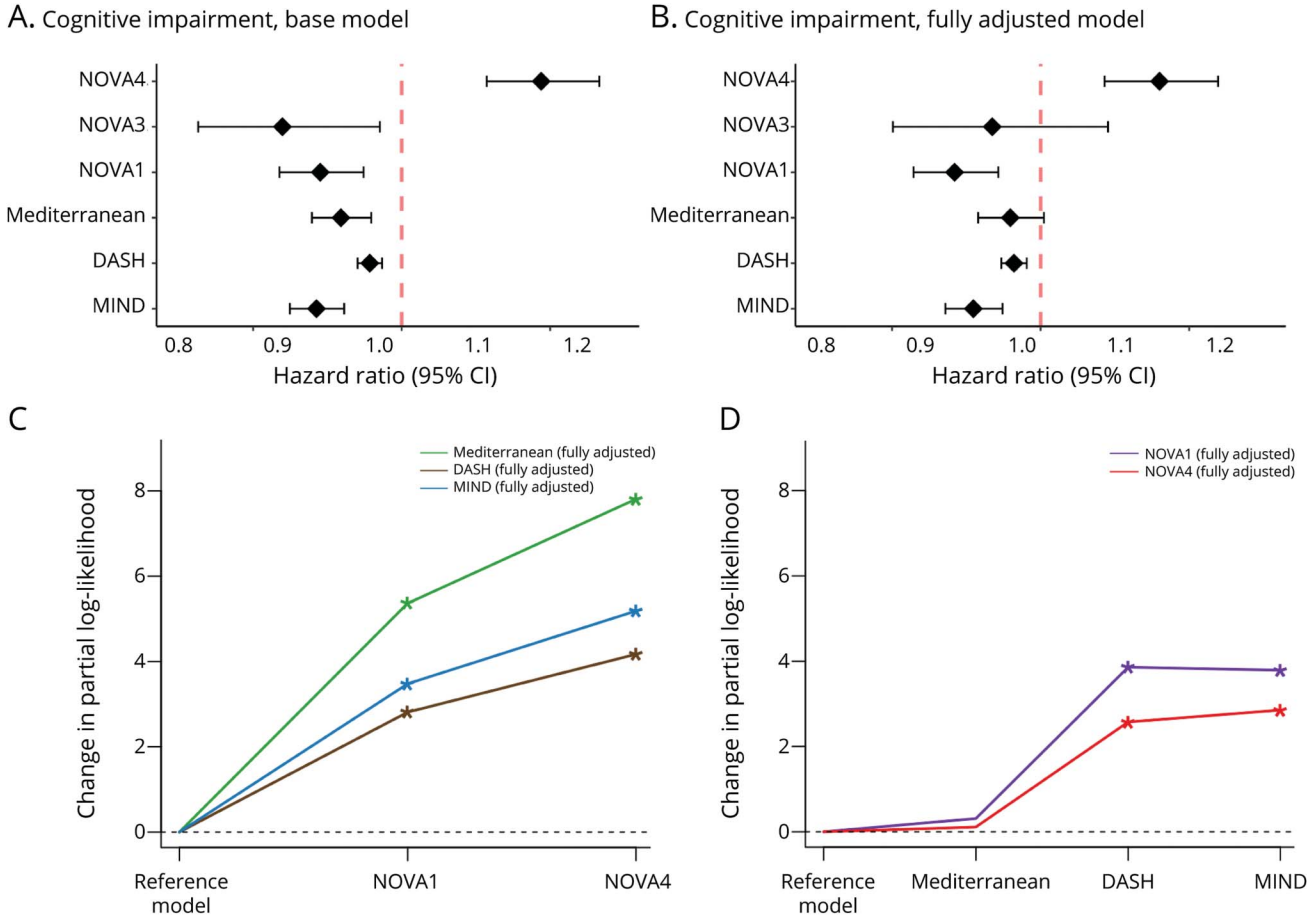
## Incident Cognitive Impairment

We next compared the risk of cognitive impairment associated with intake across NOVA categories to the effects associated with the Mediterranean, DASH, and MIND diets.

After adjustment for age, race, sex, educational attainment, annual income, and total caloric intake (base model), greater NOVA4 consumption (HR = 1.19, 95% CI 1.11–1.27, $p = 1.26 \times 10^{-7}$) was associated with increased risk of incident cognitive impairment while NOVA1 consumption (HR = 0.89, 95% CI 0.84–0.95, $p = 3.42 \times 10^{-4}$) was associated with decreased risk of cognitive impairment (Figure 3A). NOVA4 intake remained associated with cognitive impairment (HR = 1.16, 95% CI 1.09–1.24, $p = 1.01 \times 10^{-5}$) after adjustment for additional risk factors, including physical exercise, BMI category, hypertension, diabetes mellitus, cardiovascular disease, depressive symptoms, alcohol use, and smoking status (fully adjusted model). Similarly, NOVA1 intake remained associated with reduced risk of cognitive impairment (HR = 0.88, 95% CI 0.83–0.94, $p = 1.83 \times 10^{-4}$) in the fully adjusted model (Figure 3B, eTable 6). NOVA3 intake was associated with reduced cognitive impairment risk in the base model, but this effect was not significant in the fully adjusted model. NOVA2 intake was not associated with cognitive impairment in either model (eTable 6).

Greater adherence to a Mediterranean diet (HR = 0.92, 95% CI 0.88–0.96, $p = 1.20 \times 10^{-4}$), DASH diet (HR = 0.96, 95% CI 0.94–0.97, $p = 6.03 \times 10^{-7}$), and MIND diet (HR = 0.89, 95% CI 0.85–0.92, $p = 7.31 \times 10^{-9}$) was associated with reduced risk of cognitive impairment in the base model (Figure 3A). In the fully adjusted model, the DASH (HR = 0.96, 95% CI 0.95–0.98, $p = 5.41 \times 10^{-5}$) and MIND (HR = 0.91, 95% CI 0.87–0.95, $p = 1.08 \times 10^{-5}$) diets remained associated with lower risk of cognitive impairment (Figure 3B, eTable 6). Notably, no effect modification by race was observed for associations between dietary indices and cognitive impairment (eTable 6).

**Figure 3** Association Between Ultra-Processed Food Intake and Incident Cognitive Impairment




(A and B) Forest plots demonstrating hazard ratios (HR) and 95% confidence intervals (CI) for the risk of incident cognitive impairment associated with intake of NOVA1 (unprocessed or minimally processed), NOVA3 (processed), and NOVA4 (ultra-processed) items, along with higher Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet scores. HRs for NOVA categories represent the HR per 10% relative increase in consumption (in % grams/d). HRs for other dietary patterns represent the HR per 1-point increase in score. Forest plots are shown for (A) a base model, adjusted for age, race, sex, educational attainment, annual income, and total caloric intake and (B) a fully adjusted model, which also included physical exercise, body mass index category, hypertension, diabetes mellitus, cardiovascular disease, depressive symptoms, alcohol use, and smoking status. (C) Change in partial log-likelihood associated with adding NOVA1 or NOVA4 intake to reference Cox models that included adherence to a Mediterranean, DASH, or MIND diet and covariates from the fully adjusted model. Points labeled with an asterisk (*) represent significant ($p < 0.05$) changes from the reference model partial log-likelihood. (D) Change in partial log-likelihood associated with adding adherence to a Mediterranean, DASH, or MIND diet to reference Cox models that included NOVA1 or NOVA4 intake and covariates from the fully adjusted model.

We explored whether alterations in the risk of incident cognitive impairment associated with food processing were independent of other dietary scores. Adding NOVA1 or NOVA4 intake to base and fully adjusted models that included adherence to the Mediterranean, DASH, or MIND diets resulted in increased partial log-likelihood (Figure 3C). Adding DASH or MIND diet scores to base and fully adjusted models that included NOVA1 or NOVA4 intake also resulted in increased partial log-likelihood (Figure 3D, eTable 7). Consistent with these results, associations between NOVA1 or NOVA4 intake and cognitive impairment persisted in base and fully adjusted models that included the Mediterranean, DASH, or MIND diets. Associations between the DASH and MIND diets and cognitive impairment also persisted after adjustment for NOVA1 or NOVA4 consumption (Table 3). However, there were no significant interactions between NOVA1 or NOVA4 consumption and the Mediterranean, DASH, or MIND dietary patterns (eTable 8).

## Sensitivity Analyses

We conducted a variety of sensitivity analyses to assess the robustness of our findings. To determine the effect of using an energy ratio rather than a weight ratio on associations between intake across NOVA categories and incident stroke or cognitive impairment, we normalized daily caloric intake for each NOVA category to total calories consumed. While associations between UPF intake and incident cognitive impairment were replicated in the base model (HR = 1.13, 95% CI 1.06–1.20, $p = 1.06 \times 10^{-4}$) and fully adjusted model (HR = 1.09, 95% CI 1.02–1.16, $p = 7.58 \times 10^{-3}$), there was no significant association between UPF consumption and incident stroke (eTable 9). Notably, the majority of food and drink items were present in significantly different abundances when using an energy ratio rather than a weight ratio; the largest absolute differences were observed with beverages (e.g., coffee/tea, soft drinks, juice, milk) and calorically dense items (e.g., peanuts, mayonnaise, salad dressing, cookies) (eTable 10). Given the possibility that certain prevalent diagnoses might prompt participants to change their dietary habits, we examined associations between dietary indices and neurologic outcomes after excluding patients with either cardiovascular disease or diabetes. We found generally consistent associations between dietary indices and stroke (eTable 11) and cognitive impairment (eTable 12) in this sensitivity analysis. Associations between dietary indices and stroke or cognitive impairment were also similar after excluding participants who developed incident stroke or cognitive impairment after less than 2 years of follow-up (eTable 13).

We performed additional sensitivity analyses specific to the stroke or cognitive impairment outcomes. First, the inclusion of additional covariates (i.e., BMI category, alcohol use, physical activity) beyond the Framingham risk factors[31] did not alter associations between dietary indices and incident stroke (eTable 14). Second, we confirmed that the risk of cognitive impairment associated with NOVA1 and NOVA4 intake—along with adherence to the Mediterranean, DASH, and MIND diets—was similar with exclusion of follow-up

**Table 3** Associations Between Dietary Indices and Incident Cognitive Impairment after Adjustment for Other Dietary Indices

| | | Base model | | Fully adjusted model | |
|---|---|---|---|---|---|
| **Dietary index of interest** | **Dietary index (adjusted for)** | **HR (95% CI)** | ***p* Value** | **HR (95% CI)** | ***p* Value** |
| **NOVA1** | Mediterranean | 0.90 (0.85–0.96) | $2.36 \times 10^{-3}$ | 0.89 (0.83–0.95) | $7.65 \times 10^{-4}$ |
| **NOVA4** | Mediterranean | 1.17 (1.09–1.25) | $5.21 \times 10^{-6}$ | 1.16 (1.08–1.24) | $4.01 \times 10^{-5}$ |
| **Mediterranean** | NOVA1 | 0.93 (0.89–0.98) | $4.43 \times 10^{-3}$ | 0.98 (0.93–1.03) | 0.430 |
| **Mediterranean** | NOVA4 | 0.94 (0.90–0.99) | $2.11 \times 10^{-2}$ | 0.99 (0.94–1.04) | 0.636 |
| **NOVA1** | DASH | 0.93 (0.87–1.00) | $4.42 \times 10^{-2}$ | 0.92 (0.85–0.98) | $1.58 \times 10^{-2}$ |
| **NOVA4** | DASH | 1.14 (1.06–1.22) | $5.51 \times 10^{-4}$ | 1.12 (1.04–1.21) | $3.03 \times 10^{-3}$ |
| **DASH** | NOVA1 | 0.96 (0.94–0.98) | $2.93 \times 10^{-4}$ | 0.97 (0.95–0.99) | $5.54 \times 10^{-3}$ |
| **DASH** | NOVA4 | 0.97 (0.95–0.99) | $6.23 \times 10^{-3}$ | 0.98 (0.95–1.00) | $2.33 \times 10^{-2}$ |
| **NOVA1** | MIND | 0.92 (0.86–0.99) | $2.16 \times 10^{-2}$ | 0.91 (0.85–0.97) | $7.09 \times 10^{-3}$ |
| **NOVA4** | MIND | 1.14 (1.07–1.23) | $1.96 \times 10^{-4}$ | 1.13 (1.05–1.21) | $8.98 \times 10^{-4}$ |
| **MIND** | NOVA1 | 0.91 (0.86–0.95) | $4.83 \times 10^{-5}$ | 0.93 (0.89–0.98) | $6.04 \times 10^{-3}$ |
| **MIND** | NOVA4 | 0.92 (0.88–0.97) | $7.20 \times 10^{-4}$ | 0.94 (0.90–0.99) | $1.71 \times 10^{-2}$ |

Abbreviations: CI = confidence interval; DASH = Dietary Approaches to Stop Hypertension; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.
Hazard ratios (HRs) for the dietary index in the first column are shown after adjustment for the dietary index indicated in the second column. NOVA1 and NOVA4 intake were compared with other healthy dietary patterns given the associations between these NOVA categories and cognitive impairment. Multivariable Cox proportional hazards models were adjusted for age, race, sex, educational attainment, annual income, and total caloric intake (base model) and further adjusted for physical exercise, body mass index category, hypertension, diabetes mellitus, cardiovascular disease, depressive symptoms, alcohol use, and smoking status (fully adjusted model).

time points after incident stroke events (eTable 15). Third, we investigated whether dietary indices modulated the rate of change in cognitive performance with advancing age.[17] This alternative approach to assess alterations in cognition as a function of dietary habits does not require defining cognitive impairment per se. In mixed-effects models, greater NOVA4 intake (as a percentage of total grams or calories consumed) was associated with accelerated cognitive decline in base and fully adjusted models for each of 4 memory and fluency assessments. Greater NOVA1 consumption and adherence to the Mediterranean, DASH, or MIND diets were associated with slowed cognitive decline in base and fully adjusted models across all assessments (eTable 16).

## Discussion

While a healthy diet is important in maintaining brain health among older adults, the most impactful dietary exposures in the context of neurologic outcomes remain unclear. We found that increased consumption of UPFs was associated with a higher risk of both incident stroke and cognitive impairment, and the association between UPFs and incident stroke was greater among Black participants. These associations were independent of demographic, clinical, and behavioral risk factors and other dietary patterns previously associated with each outcome. Our findings support the hypothesis that the degree of food processing plays an important role in overall brain health and provides complementary information to other recommended dietary patterns, including the Mediterranean, DASH, and MIND diets.

Our study cohort and design have several strengths. The REGARDS study has a unique biracial composition, which facilitated identification of potential differences in excess stroke risk attributable to UPFs. For example, a diet characterized by the intake of fried foods, processed meats, and sugary beverages has been associated with excess incident hypertension, which in turn confers a greater risk of stroke among those who consume that diet.[33-35] The REGARDS cohort is also enriched for participants in the geographic "Stroke Belt" and is characterized by a relatively high prevalence of stroke and dementia-associated risk factors.[18,19] These features make the cohort well suited for assessing UPFs in a higher risk US population and contrast with relatively healthy cohorts in which UPFs have previously been studied (e.g., NutriNet-Santé and UK Biobank[15,36]). Furthermore, we focused on well-studied dietary patterns with predetermined scoring systems rather than dietary patterns derived using data-driven approaches.[26,37] This could facilitate external validation of our findings, and differences in adverse outcomes associated with differential adherence to dietary patterns may be conserved despite systematic variation in dietary habits across cohorts.

Our results are also subject to several important limitations. Our results differed considerably when using an energy ratio rather than a weight ratio, particularly for incident stroke, and the variable densities of different food and drink items are one limitation to choosing a weight ratio. However, an energy ratio does not account for processed foods with few or no calories and non-nutritional alterations associated with food processing. As a result, a weight ratio has often been chosen for primary analyses in observational studies on UPFs.[38-40] Because the proportion of most items in the diets of REGARDS participants differed depending on the ratio, future studies are necessary to compare the predictive power of different measures of relative dietary intake—based on grams, calories, or item-specific serving sizes—in the context of disease risk. In addition, whether the NOVA classification system adequately captures food processing differences is controversial[41] although the NOVA system remains the most widely used approach for that purpose. The accuracy of self-reported dietary information from FFQs is also known to be limited by selective energy underreporting.[42] Finally, the observational study design does not permit making causal claims. Clinical trials have sometimes complemented observational studies in demonstrating a neuroprotective role for dietary patterns such as the Mediterranean diet.[43,44] However, one recent clinical trial found that a MIND diet had no effect in preventing cognitive decline among older adults at higher risk of dementia.[45] Randomized trials can, nonetheless, be limited by shorter follow-up durations and variable conclusions depending on the efficacy of control interventions.[45]

Our findings suggest several avenues for future studies. Analyses of broad dietary indices leave open questions surrounding which food components or specific items contribute most significantly to the independent effects associated with NOVA categories in relation to other dietary patterns. These questions can be challenging to investigate because relative NOVA4 intake generally trades off directly with NOVA1 intake, given the predominance of these 2 categories in typical diets.[17] Cognitive impairment is also a complex outcome that can reflect a number of distinct causes, including stroke. Careful regression modeling may enable identifying associations between UPFs or additional dietary patterns and the severity or trajectory of poststroke cognitive impairment.[32,46] Ultimately, the core findings from this work will need to be validated in dietary intervention studies, which to date are lacking on UPFs.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