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Association of dietary protein consumption with incident silent cerebral infarcts and stroke: the ARIC Study

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Abstract

Background and Purpose—The effect of dietary protein on the risk of stroke has shown inconsistent results. We aimed to evaluate the relationship of dietary protein sources with the risk of stroke and silent cerebral infarcts in a large community based cohort.

Methods—We studied 11,601 adults (age 45–64 at baseline in 1987–1989) enrolled in the Atherosclerosis Risk in Communities (ARIC) Study, free of diabetes mellitus and cardiovascular disease. Dietary protein intake was assessed with validated food frequency questionnaires at baseline and after 6 years of follow-up. Incident stroke events were identified through hospital discharge codes and stroke deaths and physician-adjudicated through December 31, 2011. A subset of participants (n = 653) underwent brain MRI imaging in 1993–1995 and in 2004–2006. Cox proportional hazard models and logistic regression were used for statistical analyses.

Results—During a median follow-up of 22.7 years, there were 699 stroke events. In multivariable analyses, total, animal and vegetable protein consumption was not associated with risk for stroke. Red meat consumption was associated with increased stroke risk, particularly ischemic events. The hazard ratios [95% confidence intervals] for risk of ischemic stroke across ascending quintiles of red meat consumption were 1 [ref], 1.13 [0.85–1.49], 1.44 [1.09–1.90], 1.33

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Disclosures

None

[0.99–1.79], 1.47 [1.06–2.05], p_{trend} = 0.01. No association of major dietary protein sources with silent cerebral infarcts was detected.

Conclusions—This study supports the notion that consumption of red meat may increase the risk for ischemic stroke. No association between dietary protein intake and silent cerebral infarcts was found.

Keywords

dietary protein; stroke; silent cerebral infarct; community study

Introduction

The relationship of dietary protein consumption with risk of stroke has shown inconsistent results. Moderate dietary protein intake of animal origin has been associated with a lower risk of stroke while major animal sources of dietary protein such as red meat have been related to an increased risk.[1–3] These inconsistencies may be explained by a previous focus on nutrients (‘dietary protein type’) instead of food groups, which provide a more adequate assessment of the complexities of diet-disease associations. Dietary protein sources vary in their non-protein constituents (e.g. fat and sodium content), which may in part explain differential health effects. However, evidence derived from comprehensive food group analyses in community-based studies is sparse. Most current data originate from well-educated, ethnically homogenous study populations such as health professionals or selected Swedish populations.[3–5] Thus, generalizability of the existing data to more diverse populations is limited. Conclusions regarding the relation of dietary protein sources with stroke risk in the general population are difficult to draw.

Prior to clinically recognized stroke events, dietary protein intake may already have subclinical effects identified via incidence of silent cerebral infarcts (SCIs), an independent risk factor for developing symptomatic stroke events.[6–8] Whether dietary protein consumption affects the risk of SCIs is largely unknown.[9]

The objective of this study was to evaluate the relationship between total, animal, and plant-derived dietary protein, as well as more specific protein-rich food groups such as red and processed meat consumption, with the risk of stroke (hemorrhagic and ischemic) and SCIs in a large, community-based cohort of middle-aged adults.

Methods

Study Population

The Atherosclerosis Risk in Communities Study (ARIC) is a community-based prospective cohort study of 15,792 middle-aged adults (age 45–64 years at baseline) from four U.S. communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and suburbs of Minneapolis, MN).[10] For this analysis, only white and black adults were included; blacks from the Minneapolis and Washington County field centers were excluded due to small numbers. Individuals with self-reported diabetes, fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL or use of diabetes medication; a history of myocardial infarction, stroke, heart failure, coronary bypass surgery, or angioplasty; or with missing data on covariates of interest were not included. Individuals with diabetes and cardiovascular disease were not included as these conditions may lead to changes in diet. Last, participants with incomplete dietary information or with extreme caloric intake (<600 kcal or >4200 kcal per day for men, <500 kcal or >3600 kcal per day for women) were excluded from further analysis.[3] Our final study population included 11,601 persons.

The ARIC study was approved by the Institutional Review Boards (IRB) of all participating institutions, including the IRBs of the University of Minnesota, Johns Hopkins University, University of North Carolina, University of Mississippi Medical Center, and Wake Forest University. Written documentation of informed consent was obtained from all participants at each clinical site.

Assessment of dietary protein intake

The ARIC study assessed protein intake using an interviewer-administered, 66-item food frequency questionnaire (FFQ) adapted from the 61-item FFQ developed by Willett et al.[11] The FFQ was administered to all participants at visit 1 (baseline, 1987–1989) and at visit 3 (1993–1995). The residual method was applied to adjust for total energy intake.[12] For determining dietary intake, we divided participants into quintiles of cumulative average intake of various protein sources. Cumulative updating of the FFQ (i.e. visit 1 FFQ for follow-up between visit 1 and visit 3 and the average of visits 1 and 3 FFQ afterwards for those who attended both examinations, or visit 1 FFQ for those who did not attend visit 3) were used to reduce within-person variation and best represent long-term dietary behavior.[13]

Assessment of stroke events

The primary endpoint for this study was stroke (definite or probable ischemic or hemorrhagic) after the completion of the first FFQ (between 1987 and 1989). The ARIC study identified incident stroke cases through hospital discharge codes and stroke deaths.[14–16] Physician reviewers adjudicated all possible strokes and classified them as definite or probable ischemic or hemorrhagic events based on information abstracted from the medical record.[14–16] Follow-up for stroke events was available until December 31, 2011.

Brain MRI and Subclinical Cerebral Infarcts

A subset of ARIC study participants (ARIC Brain MRI study) who were 55 years or older were invited for a brain MRI during visit 3 (1993–1995) and a second brain MRI examination which took place in 2004 to 2006.[17, 18] Brain MRIs were performed using 1.5-tesla scanners and contiguous axial images 5 mm thick were obtained.[17, 18] Interpretation was done at the ARIC MRI Reading Center. SCIs were defined as focal, non-mass lesions ≥ 3mm that were bright on T2 and proton density and dark on T1 images. Further details of the MRI scanning protocol have been described previously.[17, 18]

A total of 1,945 participants successfully underwent brain MRI at visit 3, 1,812 of whom had scans of sufficient quality. A total of 906 participants (60.6% women and 48.3% blacks) received MRI imaging both at visit 3 and from 2004 to 2006. For this analysis, we examined incident SCIs in participants without evidence of SCIs or stroke history at visit 3. Our final study population consisted of 653 individuals.

Measurement of participant characteristics

Height, weight, and waist circumference were measured following a standardized protocol.[10, 19] Data on smoking, ethanol intake, education, intake of antihypertensive or lipid-lowering medication were derived from standardized questionnaires.[10] ARIC participants underwent fasting venipuncture at each examination.[10] Sports-related physical activity and leisure-related physical activity were assessed with the use of Baecke's questionnaire and scoring systems.[20] Depressive symptoms were assessed using a 21-item questionnaire on 'vital exhaustion' developed by Appels et al..[21] Diabetes was defined as current use of glucose-lowering medications, fasting blood glucose ≥ 126 mg/dL, non-fasting blood glucose ≥ 200 mg/dL or self-reported history of diabetes. Hypertension was defined based on the average of the last two of three blood pressure readings, as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

Statistical Analysis

To assess the association of total, animal and vegetable protein intake with incidence of stroke and SCIs, we calculated incidence rates (IR) of stroke events per 1,000 person-years as the number of diagnosed cases occurring during the entire follow-up period divided by person-years of follow-up. Follow-up time was defined as time from the baseline examination to the earliest of the first event, death, lost to follow-up, or December 31, 2011. Multivariable Cox proportional hazards regression models were used to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of total, ischemic, and hemorrhagic stroke by quintiles of the dietary exposure, using the lowest quintile as the reference. Similarly, logistic regression was used to calculate odds ratios (OR) and 95% CIs of incident SCI by quartiles of protein intake. An initial model adjusted for age, race, sex, ARIC study center, and total energy intake (minimally adjusted model, Model 1). A second model additionally adjusted for smoking (current, former, never), pack years of smoking, education (less than high school, high school, more than high school), systolic blood pressure (mmHg), use of antihypertensive medication, HDL cholesterol (mmol/l), total cholesterol (mmol/l), use of lipid lowering medication, body mass index (kg/m^2), waist-to-hip ratio, alcohol intake (g/week), Baecke's physical activity score, leisure-related physical activity, carbohydrate intake (quintiles), fiber intake (quintiles), dietary fat (quintiles) and magnesium intake (quintiles) (fully adjusted model, Model 2). Median protein intake of each quintile (g/d) were modeled as a continuous variable to test for linear trend. Tests of the proportional hazards assumption were evaluated through the examination of an interaction term between each protein variable and follow-up time along with the inspection of log-negative log survival curves; no violations from the assumption were observed. All statistical tests were 2-tailed. Data were analyzed with SAS 9.3 (SAS Corp, Cary, NC).

Results

Baseline characteristics of the study participants according to quintiles of total protein intake are shown in Table 1. Compared with participants with high protein consumption, individuals with low protein consumption were more likely to be black, to be a current smoker and less likely to have graduated from high school or to be less physically active. Participants with low protein intake were more likely to have a lower BMI and a higher systolic blood pressure; they were less likely to be using lipid-lowering medication, consumed more carbohydrates and alcohol but less fiber. Across dietary protein quintiles, we found no differences in age, gender, energy intake, blood lipids or prevalence of hypertension.

During a median follow-up of 22.7 years, there were 699 total stroke events among 11,601 participants. When analyzing the association of dietary protein type with stroke incidence, neither total protein intake nor animal protein consumption was significantly related to total stroke events (Table 2), or hemorrhagic or ischemic stroke incidents (Supplemental Table I). In the minimally adjusted model, higher intake of vegetable sources of protein was significantly associated with a 21% reduced risk of incident stroke ($HR_{Q5\ vs.\ Q1}$: 0.79, 95% CI: 0.61, 1.00; $p\text{-}_{for\text{-}trend}$=0.03; Table 2). However, this association was no longer significant in the fully adjusted model (Table 2) and according to stroke sub-types (Supplemental Table I). Results were essentially the same once we accounted for depressive symptoms (Supplemental Table II) as well as once we included animal and vegetable protein simultaneously in the model (data not shown).

In detailed food-group analyses of major dietary protein sources (Table 3), higher intake of processed meat and red meat was significantly associated with an increased risk for total stroke ($HR_{Q5\ vs.\ Q1}$: 1.24; 95% CI, 0.94, 1.63, p_{trend}=0.04 for processed meat; $HR_{Q5\ vs.\ Q1}$: 1.41, 95% CI, 1.04, 1.92, p_{trend}=0.01 for red meat). Low-fat dairy and egg consumption were associated with a decreased risk for stroke in the minimally adjusted model, but these associations were attenuated and became insignificant after full adjustment for potential confounders. In stroke subtype analyses (Supplemental Table III), among dietary protein sources higher egg consumption was found to be associated with risk for hemorrhagic stroke ($HR_{Q5\ vs.\ Q1}$: 1.41, 95% CI, 0.77, 2.57, p_{trend}=0.02) whereas only red meat consumption was related to ischemic stroke events ($HR_{Q5\ vs.\ Q1:}$1.47, 95% CI, 1.06, 2.05, p_{trend}=0.01). When we investigated the association of major dietary protein sources with stroke incidence by sex (Supplemental Table IV), we found red and processed meat consumption to be associated with an increased risk for male participants ($HR_{Q5\ vs.\ Q1}$: 1.62, 95% CI, 1.03, 2.57, p_{trend}=0.03).

During a median follow-up of 10.4 years, there were 127 SCIs among 653 participants. We did not observe any association between dietary protein type and risk for SCIs (Table 4). In food-group analyses (Supplemental Table V), nuts and low-fat dairy consumption were significantly associated with decreased risk for SCIs after minimal adjustment, but none of these associations remained significant after fully accounting for confounding factors. Poultry intake was not associated with incident SCIs after minimally adjusting, but became significant after fully adjusting for confounding factors (OR_{Q4}: 1.93, 95% CI, 1.02, 3.67; p_{trend}=0.05).

Discussion

In a large community-based study population, we did not find dietary protein type but more specific protein sources such as red meat and processed meat to be associated with an increased risk for total stroke events. This elevation of risk was mainly driven by an association of red meat intake with ischemic stroke cases. Neither dietary protein type nor protein sources were associated with SCIs.

Most recently a large meta-analysis suggested that moderate dietary protein intake in particular of animal origin was associated with a lower risk for stroke events, but this risk may differ by the specific protein source consumed.[2] To this point, the largest and most comprehensive investigation to examine an association between protein intake and stroke was undertaken using data from the Nurses' Health Study and Health Professionals Follow-up Study.[3] Higher intake of red meat was associated with an elevated risk for stroke, whereas higher intake of poultry was associated with a lower risk. Similarly, in Swedish men and women, higher intake of red and processed meat products was found to be associated with ischemic infarcts.[4, 5] Our data support the notion that high consumption of red and processed meat products do significantly impact stroke risk in a general Western community setting. Other major dietary protein sources such as fish, low-fat dairy, and nut consumption have been inversely associated with stroke risk in previous reports[22–25], whereas dietary legumes or egg intake were not found to be related to stroke risk.[22, 23, 26, 27] In our cohort, we did observe a decreased stroke risk with low-fat dairy consumption whereas egg consumption appeared to increase stroke risk, but none of these findings remained significant after full adjustment for confounding variables. The increased risk of hemorrhagic stroke associated with higher egg consumption in subgroup analyses contradicts previous analysis and warrants further studies since this subgroup finding was based on a rather small number of events.[27]

SCIs do not cause acute symptoms and are clinically unrecognized. Nonetheless, these abnormalities are not benign, appear more common with advancing age and are associated with a future risk of stroke.[6, 28] In our middle-aged population approximately 20% of participants developed SCIs over a 10 year period. We did not observe any association between dietary protein type and SCIs. Among protein sources, dietary fish with higher dietary eicosapentaenoic and docosahexaenoic acid content has been reported to be associated with lower incidence of SCIs.[9] Our results indeed suggest that higher fish, nuts, or low-fat dairy consumption tends to be associated with lower risk for SCIs. However, these findings have to be interpreted with caution as the number of SCIs was small, and individual results may be spurious.

Mechanisms that explain varying associations of dietary protein sources with stroke risk are numerous. Most importantly, processed meat is known to contain a high sodium amount, which is strongly correlated with incident hypertension.[29, 30] Heme iron intake and serum ferritin concentrations were found to be associated with an increased risk of stroke.[31, 32] The potential adverse effect of heme iron may be attributed to its pro-oxidative properties whereas serum ferritin levels may further indicate a pro-inflammatory environment.

The strenghts of our analysis include the study of a large, biracial, community-based prospective cohort and the long follow-up with structured assessment of dietary intake, covariates, and adjudicated outcome events.[13, 33] Nonetheless, there are several limitations. Our dietary data assessment may misclassify diet as protein intake was only assessed at two time-points and changing dietary habits over time may not have been covered adequately by our FFQs. Conversely, significant behavioral dietary changes are unlikely to occur in the overall population.[34, 35] Residual and unmeasured confounding could be partly responsible for the results although we adjusted our analyses for a wide range of confounding factors. Last, intake of certain food groups such as fish as well as the number of hemorrhagic stroke events were low which may limit our analyses.

In conclusion, using a large community-based cohort study we found neither total nor animal or vegetable protein to be associated with stroke incidence. In detailed food group analyses of major protein sources, red meat consumption was related to an increased risk for ischemic stroke events. No association between dietary protein intake and silent cerebral infarcts was found.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics according to quintiles of total protein intake, ARIC 1987–1989

	Q 1 (low)	Q 2	Q 3	Q 4	Q5 (high)	p-trend[a]
N	**2320**	**2320**	**2321**	**2320**	**2320**	
Total protein intake, g/day (SD)	49.3 (10.2)	62.9 (3.9)	70.1 (3.9)	77.7 (4.0)	93.3 (12.6)	<0.0001
Total protein intake, % of total energy	12.4 (1.7)	15.7 (1.0)	17.8 (1.5)	19.8 (2.0)	22.7 (3.3)	<0.0001
Animal protein intake, g/day (SD)	32.4 (10.0)	45.2 (5.5)	51.9 (5.7)	59.7 (5.8)	75.8 (14.3)	<0.0001
Vegetable protein intake, g/day (SD)	17.0 (5.8)	17.7 (4.7)	18.2 (5.0)	18.0 (5.1)	17.6 (5.7)	<0.0001
Age, years (SD)	53.4 (5.7)	53.9 (5.7)	54.0 (5.8)	53.7 (5.7)	53.8 (5.7)	0.10
Women, %	55.9	55.9	55.9	55.9	55.9	0.99
Black, %	25.2	24.7	21.8	21.7	22.6	0.004
High school graduate or higher, %	72.8	77.8	81.1	82.8	84.5	<0.0001
Current smoker, %	32.1	28.5	24.3	22.7	21.1	<0.0001
Vital exhaustion score (SD)	11.2 (8.9)	10.1 (8.5)	9.1 (8.0)	9.1 (7.8)	9.3 (8.2)	<0.0001
Hypertension, %	29.4	27.8	28.7	28.2	28.3	0.54
Body Mass Index, kg/m^2 (SD)	26.6 (5.1)	26.8 (4.9)	27.0 (4.9)	27.3 (5.0)	27.7 (5.0)	<0.0001
Waist-to-hip ratio (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.16
Baecke Sport Activity Score (SD)	2.4 (0.8)	2.4 (0.8)	2.5 (0.8)	2.5 (0.8)	2.6 (0.8)	<0.0001
Baecke Leisure Index (SD)	2.3 (0.6)	2.3 (0.6)	2.4 (0.6)	2.4 (0.6)	2.5 (0.6)	<0.0001
Systolic blood pressure, mmHg (SD)	120.8 (18.7)	120.0 (17.7)	119.8 (17.4)	119.3 (17.7)	119.3 (18.0)	0.002
Serum HDL, mmol/L (SD)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)	0.31
Total cholesterol, mmol/L (SD)	5.5 (1.0)	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)	5.5 (1.1)	0.30
Use of antihypertensive medication, %	21.6	22.0	24.3	22.4	22.8	0.33
Use of lipid lowering medication, %	1.3	1.7	2.3	3.2	2.7	<0.0001
Carbohydrate intake, g/day (SD)	230.8 (47.4)	207.8 (31.4)	197.6 (31.4)	188.4 (32.2)	172.5 (37.9)	<0.0001
Carbohydrate intake, % of total energy (SD)	56.1 (9.5)	51.3 (7.9)	48.3 (7.7)	45.8 (7.5)	42.9 (7.7)	<0.0001
Fiber intake, g/day (SD)	15.5 (7.3)	16.7 (5.7)	17.3 (5.6)	17.6 (5.9)	18.3 (7.0)	<0.0001
Magnesium intake, mg/day (SD)	216.9 (65.6)	240.8 (52.7)	253.3 (54.1)	267.1 (57.7)	288.3 (65.5)	<0.0001
Alcohol intake, g/week (SD)	67.9 (149.2)	44.9 (90.6)	40.7 (78.7)	37.0 (70.5)	32.4 (65.0)	<0.0001

	Q 1 (low)	Q 2	Q 3	Q 4	Q5 (high)	p-trend[a]
N	**2320**	**2320**	**2321**	**2320**	**2320**	
Fish intake, servings/day (SD)	0.2 (0.1)	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)	0.5 (0.5)	<0.0001
Total energy intake, kcal/day (SD)	1814.2 (694.2)	1487.8 (555.9)	1488.7 (537.5)	1566.3 (535.9)	1799.9 (603.7)	0.21
Total fat Intake, g/day (SD)	53.9 (16.1)	59.7 (11.6)	61.3 (12.0)	62.4 (12.8)	63.2 (15.3)	<0.0001
Total fat intake, % of total energy (SD)	30.0 (7.2)	32.4 (6.2)	33.4 (6.3)	34.1 (6.2)	34.5 (6.5)	<0.0001

Values are % for categorical variables and mean (SD) for continuous variables.

[a] p-values from general linear models for continuous variables and Mantel-Haenszel 1-degree of freedom chi-square statistic for categorical variables

Table 2

Association of total, animal and vegetable protein intake (in quintiles) with stroke incidence, ARIC 1987–2011

	Q 1	Q 2	Q 3	Q 4	Q 5	p-trend
n	**2320**	**2320**	**2321**	**2320**	**2320**	
Total Protein Intake						
Female range, g/day	<56.03	56.03–63.65	>63.65–70.81	70.82–79.57	>79.58	
Male range, g/day	<62.44	62.44–70.14	70.15–77.19	77.20–85.77	>85.78	
Events, n	141	128	146	141	143	
Person-time	46,660	47,304	47,307	47,310	47,464	
Incidence, per 1000 py	3.0	2.7	3.1	3.0	3.0	
HR (95%CI)*	1 (ref)	1.05 (0.83, 1.34)	1.14 (0.90, 1.45)	1.00 (0.78, 1.28)	1.10 (0.87, 1.39)	0.57
HR (95%CI)**	1 (ref)	1.19 (0.92, 1.54)	1.30 (0.99, 1.71)	1.17 (0.86, 1.57)	1.21 (0.87, 1.69)	0.36
Animal Protein Intake						
Female range, g/day	<38.65	38.65–46.72	46.73–53.87	53.88–63.36	>63.37	
Male range, g/day	<42.43	42.43–50.91	50.92–58.36	58.37–66.88	>66.89	
Events, n	129	130	143	152	145	
Person-time	46,726	47,517	47,323	47,422	47,058	
Incidence, per 1000 py	2.8	2.7	3.0	3.2	3.1	
HR (95%CI)*	1 (ref)	1.18 (0.93, 1.51)	1.10 (0.86, 1.41)	1.15 (0.90, 1.47)	1.20 (0.94, 1.52)	0.22
HR (95%CI)**	1 (ref)	1.32 (1.02, 1.69)	1.21 (0.93, 1.58)	1.27 (0.96, 1.69)	1.23 (0.89, 1.69)	0.31
Vegetable Protein Intake						
Female range, g/day	<13.19	13.19–15.29	>15.29–17.19	>17.19–19.78	>19.79	
Male range, g/day	<14.85	14.85–17.38	>17.38–19.61	19.62–22.92	>22.93	
Events, n	147	140	147	143	122	
Person-time	46,362	47,342	47,221	47,457	47,664	
Incidence, per 1000 py	3.2	3.0	3.1	3.0	2.6	
HR (95%CI)*	1 (ref)	0.98 (0.77, 1.24)	1.02 (0.81, 1.28)	0.91 (0.72, 1.15)	0.79 (0.61, 1.00)	0.03
HR (95%CI)**	1 (ref)	1.10 (0.86, 1.41)	1.19 (0.92, 1.53)	1.09 (0.83, 1.44)	1.02 (0.75, 1.39)	0.94

* adjusted for age, sex, race, study center, and total energy intake

** adjusted for age, sex, race, study center, total energy intake, smoking, cigarette years, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, fat intake and magnesium intake

Table 3

Association of major dietary protein sources (in quintiles) with stroke incidence, ARIC 1987 – 2011

	Q 1	Q 2	Q 3	Q 4	Q 5	p-trend
Processed Meat						
n	2333	2731	1838	2427	2272	
Events, n	122	156	116	119	186	
Median svg/day	0	0.14	0.35	0.50	1.07	
HR (95%CI)*	1 (ref)	1.18 (0.92, 1.51)	1.12 (0.86, 1.45)	1.02 (0.79, 1.32)	1.54 (1.20, 1.98)	0.0002
HR (95%CI)**	1 (ref)	1.06 (0.83, 1.36)	1.02 (0.78, 1.34)	0.86 (0.66, 1.13)	1.24 (0.94, 1.63)	0.04
Red Meat						
n	2510	2115	2506	2212	2258	
Events, n	130	107	161	154	147	
Median svg/day	0.14	0.28	0.50	0.65	1.08	
HR (95%CI)*	1 (ref)	1.15 (0.89, 1.48)	1.43 (1.12, 1.82)	1.51 (1.18, 1.94)	1.65 (1.26, 2.15)	<0.0001
HR (95%CI)**	1 (ref)	1.13 (0.87, 1.47)	1.37 (1.06, 1.77)	1.38 (1.05, 1.81)	1.41 (1.04, 1.92)	0.01
Red Meat & Processed Meat						
n	2379	2290	2314	2289	2329	
Events, n	106	126	157	139	171	
Median svg/day	0.25	0.54	0.85	1.21	1.90	
HR (95%CI)*	1 (ref)	1.27 (0.98, 1.64)	1.58 (1.23, 2.04)	1.38 (1.06, 1.81)	1.78 (1.35, 2.35)	<0.0001
HR (95%CI)**	1 (ref)	1.15 (0.88, 1.51)	1.39 (1.06, 1.81)	1.13 (0.84, 1.52)	1.38 (1.00, 1.91)	0.06
Poultry						
n	1663	3163	1344	3176	2255	
Events, n	111	185	76	208	119	
Median svg/day	0.07	0.14	0.28	0.43	0.80	
HR (95%CI)*	1 (ref)	0.92 (0.73, 1.17)	0.73 (0.55, 0.97)	0.87 (0.68, 1.11)	0.78 (0.60, 1.01)	0.12
HR (95%CI)**	1 (ref)	0.90 (0.71, 1.15)	0.87 (0.65, 1.15)	0.90 (0.70, 1.16)	0.86 (0.65, 1.14)	0.55
Dairy						

	Q 1	Q 2	Q 3	Q 4	Q 5	p-trend
n	2367	2299	2326	2259	2350	
Events, n	162	154	122	135	126	
Median svg/day	0.14	0.57	1.07	1.50	2.86	
HR (95%CI)*	1 (ref)	1.02 (0.82, 1.28)	0.73 (0.57, 0.93)	0.85 (0.67, 1.08)	0.79 (0.61, 1.03)	0.04
HR (95%CI)**	1 (ref)	1.12 (0.89, 1.40)	0.78 (0.61, 1.00)	0.93 (0.73, 1.20)	0.86 (0.65, 1.15)	0.15
High-Fat Dairy						
n	2298	2335	2547	2173	2248	
Events, n	136	129	165	137	132	
Median svg/day	0.07	0.14	0.43	0.80	1.23	
HR (95%CI)*	1 (ref)	1.02 (0.80, 1.29)	1.17 (0.93, 1.49)	1.02 (0.80, 1.31)	0.99 (0.77, 1.28)	0.85
HR (95%CI)**	1 (ref)	1.05 (0.82, 1.33)	1.17 (0.92, 1.49)	1.06 (0.82, 1.36)	0.92 (0.71, 1.20)	0.37
Low-Fat Dairy						
n	3130	1649	2181	2439	2202	
Events, n	213	117	126	131	112	
Median svg/day	0	0.07	0.43	1.00	2.50	
HR (95%CI)*	1 (ref)	1.11 (0.89, 1.39)	0.81 (0.64, 1.03)	0.86 (0.68, 1.09)	0.74 (0.57, 0.96)	0.005
HR (95%CI)**	1 (ref)	1.26 (1.00, 1.58)	1.01 (0.79, 1.28)	1.04 (0.81, 1.33)	0.91 (0.68, 1.21)	0.13
Fish & Seafood						
n	2076	3227	1795	2092	2411	
Events, n	112	203	108	131	145	
Median svg/day	0	0.14	0.21	0.28	0.57	
HR (95%CI)*	1 (ref)	1.06 (0.84, 1.33)	0.90 (0.70, 1.16)	0.92 (0.72, 1.17)	0.91 (0.71, 1.15)	0.27
HR (95%CI)**	1 (ref)	1.08 (0.86, 1.36)	0.97 (0.75, 1.26)	0.98 (0.76, 1.26)	0.95 (0.73, 1.24)	0.46
Eggs						
n	2077	2127	2885	3189	1322	
Events, n	121	92	169	218	99	
Median svg/day	0	0.07	0.14	0.43	1.00	
HR (95%CI)*	1 (ref)	0.81 (0.62, 1.07)	1.09 (0.86, 1.37)	1.15 (0.90, 1.47)	1.23 (0.97, 1.56)	0.01

	Q 1	Q 2	Q 3	Q 4	Q 5	p-trend
HR (95%CI)**	1 (ref)	0.79 (0.60, 1.04)	1.05 (0.83, 1.33)	1.03 (0.80, 1.32)	1.08 (0.84, 1.39)	0.19
Nuts & Peanut Butter						
n	1951	2842	2363	2183	2262	
Events, n	130	155	138	141	135	
Median svg/day	0	0.07	0.21	0.43	1.00	
HR (95%CI)*	1 (ref)	0.79 (0.63, 1.01)	0.93 (0.73, 1.19)	0.92 (0.72, 1.17)	0.86 (0.67, 1.11)	0.74
HR (95%CI)**	1 (ref)	0.83 (0.65, 1.05)	1.03 (0.81, 1.32)	1.04 (0.81, 1.33)	1.00 (0.77, 1.31)	0.42
Legumes						
n	2767	2771	828	2853	2382	
Events, n	131	164	47	189	168	
Median svg/day	0.07	0.14	0.21	0.28	0.57	
HR (95%CI)*	1 (ref)	1.05 (0.82, 1.34)	1.14 (0.88, 1.47)	1.08 (0.84, 1.39)	1.15 (0.90, 1.49)	0.42
HR (95%CI)**	1 (ref)	1.07 (0.84, 1.37)	1.16 (0.89, 1.51)	1.18 (0.91, 1.53)	1.29 (0.98, 1.70)	0.10

* adjusted for age, sex, race, study center, and total energy intake

** adjusted for age, sex, race, study center, total energy intake, smoking, cigarette years, education, systolic blood pressure, use of antihypertensive medication, HDLc, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, fat intake and magnesium intake

Table 4

Association of total, animal and vegetable protein intake (in quartiles) with incidence of silent cerebral infarcts, ARIC 1993–2006

	Q 1	Q 2	Q 3	Q 4	p-trend
n	**162**	**164**	**164**	**163**	
Total Protein Intake					
Female range, g/day	<60.46	60.46–68.99	69.00–77.19	≥77.20	
Male range, g/day	<67.87	67.87–76.23	76.24–85.46	≥85.47	
Events, n	32	39	28	28	
OR (95%CI)*	1 (ref)	1.13 (0.66, 1.94)	0.76 (0.42, 1.34)	0.83 (0.47, 1.47)	0.35
OR (95%CI)**	1 (ref)	1.17 (0.62, 2.20)	0.73 (0.35, 1.50)	0.89 (0.39, 2.04)	0.65
Animal Protein Intake					
Female range, g/day	<42.67	42.67–51.00	51.01–59.87	≥59.88	
Male range, g/day	<47.92	47.92–55.28	55.29–66.23	≥66.24	
Events, n	34	33	34	26	
OR (95%CI)*	1 (ref)	0.88 (0.51, 1.52)	0.91 (0.53, 1.57)	0.72 (0.41, 1.28)	0.29
OR (95%CI)**	1 (ref)	1.00 (0.54, 1.85)	0.97 (0.49, 1.89)	0.80 (0.36, 1.79)	0.60
Vegetable Protein Intake					
Female range, g/day	<14.73	14.73–16.79	16.80–20.00	≥20.01	
Male range, g/day	<17.07	17.07–19.19	19.20–22.22	≥22.23	
Events, n	33	32	33	29	
OR (95%CI)*	1 (ref)	0.95 (0.54, 1.67)	0.97 (0.56, 1.69)	0.81 (0.45, 1.45)	0.46
OR (95%CI)**	1 (ref)	1.15 (0.62, 2.15)	1.27 (0.64, 2.54)	0.97 (0.42, 2.23)	0.90

* adjusted for age, sex, race, study center, and total energy intake

** adjusted for age, sex, race, study center, total energy intake, smoking, cigarette years, education, systolic blood pressure, use of antihypertensive medication, HDLc, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, fat intake and magnesium intake