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Dietary Protein Sources and the Risk of Stroke in Men and Women

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Abstract

Background and Purpose—Few dietary protein sources have been studied prospectively in relation to stroke. We examined the relation between foods that are major protein sources and risk of stroke.

Methods—We prospectively followed 84,010 women aged 30–55 years at baseline and 43,150 men aged 40–75 years at baseline without diagnosed cancer, diabetes, or cardiovascular disease. Diet was assessed repeatedly by a standardized and validated questionnaire. We examined the association between protein sources and incidence of stroke using a proportional hazard model adjusted for stroke risk factors.

Results—During 26 and 22 years of follow-up in women and men, respectively, we documented 2,633 and 1,397 strokes, respectively. In multivariable analyses, higher intake of red meat was associated with an elevated risk of stroke, while a higher intake of poultry was associated with

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- Research grants for studying the effects of diet on cardiometabolic diseases from the National Institutes of Health; the Searle Scholar Award from the Searle Funds at The Chicago Community Trust; the Genes and Environment Initiative at the Harvard School of Public Health; and the Gates Foundation/World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study; and from GlaxoSmithKline, Sigma Tau, Pronova, and the National Institutes of Health for an investigator-initiated, not-for-profit clinical trial of fish oil and post-surgical complications.
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- Ad hoc consulting fees: Foodminds.
- Royalties: UpToDate, for an online chapter on fish oil.
- Patent: Harvard University has filed a provisional patent application that has been assigned to Harvard University, listing Dr. Mozaffarian as a co-inventor to the US Patent and Trademark Office for use of trans-palmitoleic acid to prevent and treat insulin resistance, type 2 diabetes, and related conditions.

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lower risk. In models estimating the effects of exchanging different protein sources, compared to one serving/day of red meat, one serving/day of poultry was associated with a 27% (95% CI: 12% to 39%) lower risk of stroke, nuts with a 17% (95% CI: 4% to 27%) lower risk, fish with a 17% (95% CI: 0% to 30%) lower risk, low-fat dairy with an 11% (95% CI: 5% to 17%) lower risk, and whole-fat dairy with a 10% (95% CI: 4% to 16%) lower risk. We did not see significant associations with exchanging legumes or eggs for red meat.

Conclusions—These data suggest that stroke risk may be reduced by replacing red meat with other dietary sources of protein.

Keywords

men; women; diet; protein; nutrition; stroke

Introduction

A diet high in protein, compared isocalorically to one high in carbohydrate, lowers blood pressure, a major risk factor for stroke, and improves plasma lipids [1]. Yet foods that are major protein sources vary greatly in their non-protein constituents and thus may have different relationships to risk of stroke, but these relationships have not been closely examined. In a recent meta-analysis of two observational studies, red meat intake was not significantly associated with incident stroke, and the paucity of data was noted [2]. Higher fish intake has been associated with a lower risk of ischemic stroke in men [3] and thrombotic stroke in women [4]. No significant associations were seen between intakes of eggs, nuts, or whole-fat dairy products [5-6] and stroke risk. Understanding which protein-rich foods are associated with stroke risk is important because substituting one for another may be easier for individuals to accomplish than substituting one nutrient for another, or one dietary pattern for another.

We have previously reported on the relation between major dietary protein sources and incident coronary heart disease (CHD) in women [7]. Higher intakes of red meat and whole-fat dairy products were associated with a higher risk of CHD, while higher intakes of nuts, fish, and poultry were associated with a lower risk. To better understand the relations between dietary protein sources and risk of stroke, we investigated these in two large prospective cohorts of men and women.

Materials and Methods

Study Populations

The Nurses' Health Study (NHS) began in 1976 when 121,700 female registered nurses aged 30–55 residing in the U.S. provided information on their medical history and lifestyle. The Health Professionals Follow-Up Study (HFPS) began in 1986 when 51,529 male dentists, pharmacists, optometrists, osteopaths, podiatrists, and veterinarians aged 40–75 years and residing in the U.S. provided information on their medical history and lifestyle. Every two years, follow-up questionnaires have been sent to update this information. In 1980, a 61-item food-frequency questionnaire (FFQ) was included to assess intake of specific foods in NHS. Expanded questionnaires updated dietary intake in 1986, 1990, 1994, 1998, and 2002. In 1986, a 131-item FFQ assessed intake of specific foods in HPFS and similar questionnaires were used to update dietary intake in 1990, 1994, 1998, 2002, and 2006. As in our previous analysis, we excluded participants with excessive blank items on their baseline FFQ, implausibly low or high energy intake, and those with previously diagnosed cancer, diabetes, angina, myocardial infarction, stroke, or other cardiovascular disease (including a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)) [7]. The final baseline populations consisted of 84,010 women and 43,150 men.

The study was approved by the Committee on the use of Human Subjects in Research at Brigham and Women's Hospital. Return of a questionnaire was considered to imply consent.

Ascertainment of Diet

To calculate intakes of specific protein sources, a commonly used unit or portion size for each food was specified on the FFQ and the participant was asked how often on average during the previous year he or she had consumed that amount, with answers ranging from "never" to "more than six times per day" (for portion sizes, see online-only Data Supplement at http://stroke.ahajournals.org). The major contributors to protein intake reported on the FFQs included: unprocessed red meat (hamburger, beef, pork, and lamb), processed red meat (beef hot dog, processed meats such as bologna and salami, and bacon), poultry (chicken with and without skin, chicken sandwich, and chicken/turkey hot dog), whole-fat dairy (whole milk, ice cream, hard cheese, full fat cheese, cream, sour cream, cream cheese, butter), and low-fat dairy (skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet). We also evaluated fish (canned tuna, dark and light fleshed fish, and breaded fish), eggs, nuts, and legumes (dry beans, peas, soy, and tofu). In sensitivity analyses, we evaluated total processed meat (processed red meat plus chicken/turkey hot dogs), poultry excluding chicken/turkey hot dogs, whole-fat dairy excluding ice cream, and low-fat dairy excluding sherbet. The reproducibility and validity of the FFQs in measuring food intake have been previously described [8–10].

Ascertainment of Stroke

When participants reported a stroke, we obtained permission to review their medical records. Stroke was classified as ischemic (thrombotic, embolic, or unspecified non-hemorrhagic), hemorrhagic, or of unknown type, according to criteria in the National Survey of Stroke [11]. Subarachnoid hemorrhages were distinguished from intraparenchymal hemorrhages. Nonfatal strokes for which confirmatory information was obtained by interview or letter but no medical records were available and no neuro-imaging was available were designated as probable (223/1098, or 20%, of cases in men and 641/2153, or 30%, of cases in women). Deaths were identified from state vital records, the National Death Index, next-of-kin, or the postal system. Stroke was confirmed as fatal by medical records or autopsy report. Fatal stroke was designated as probable if stroke was reported on the death certificate or reported by next-of-kin, but no medical records were available. These constituted 31% (93/299) of cases in men and 43% (207/480) of cases in women. We included confirmed and probable cases in our report because results were similar after probable cases were excluded.

Data Analysis

We first assessed whether intermediate outcomes (diabetes, hypertension, hypercholesterolemia, angina, or CABG/PCI) were associated with a subsequent change in dietary protein intake; these associations were weak and thus these intermediate diagnoses could not be important time-dependent confounders. Therefore, to avoid misclassification of participants' long-term diet, we continued updating each person's intake throughout follow-up using data from all repeated FFQs (see online-only Data Supplement for expanded methods at http://stroke.ahajournals.org).

Participants were divided into quintiles of cumulative average intake of major dietary protein sources to reduce within-person variation and best represent long-term diet. These averages were calculated by taking the mean of all reported FFQ intakes up to the beginning of a 2-year follow-up interval. The cumulative average intake was then used to predict stroke incidence from the time of the last returned questionnaire until the next follow up cycle. If dietary data from a particular FFQ was missing, we carried forward the most recent cumulative average value.

We evaluated associations between foods used as categorical and continuous variables and incidence of total stroke, intraparenchymal hemorrhage, and ischemic stroke. To compare with previous analyses [3–4], we evaluated the relation between fish intake less than once per month versus intake more than once per month and risk of stroke. Person-years of follow-up were calculated from the return of the baseline FFQ to the date of the first stroke event, death, or June 1, 2006 (NHS) or January 31, 2008 (HPFS), whichever came first. The relative risk (RR) was computed using a multivariable Cox proportional hazards regression model. The model was stratified on age (months) and calendar time (2-year time intervals), and included dietary protein sources (servings/day) and also intakes of total energy (Kcal), cereal fiber (g/day), alcohol (g/day), fruit and vegetables (servings/day), *trans* unsaturated fatty acids (g/day), and potential non-dietary confounding variables, which were updated biennially: body mass index (BMI, 10 categories), physical exercise (<3, 3–9, 9–18, 18–27, 27+ metabolic equivalents/week), cigarette smoking (never, past, current 1–14 cig/day, current 14–25 cig/day, current 25+ cig/day), menopausal status in women (pre-menopausal, postmenopausal with no history of hormone replacement, postmenopausal with a history of hormone replacement, postmenopausal with current hormone replacement), parental history of early myocardial infarction (before age 60), years of multivitamin use, vitamin E supplement use (yes/no), and aspirin use (yes/no). Neither the diagnoses of diabetes, angina, hypertension, hypercholesterolemia, CABG/PCI, or myocardial infarction, nor use of medications prescribed to treat these conditions (including statins and beta-blockers), were included in the multivariable models, as these may be considered intermediate outcomes on the causal pathway between diet and stroke. However, in sensitivity analyses, intermediate diagnoses were included. The median values for each quintile of cumulative average food intake were used as a single variable to test for linear trend across quintiles and to estimate the relative risk for a one-serving/day increase in intake. Relative risks and standard errors for each quintile from each cohort were pooled in fixed-effects models to calculate summary estimates.

To examine for potential effect modification of the association between stroke risk and total red meat intake by adiposity, we stratified our multivariate model on body mass index (< 25 versus ≥ 25) and, separately, tested the significance of an interaction with a likelihood ratio test comparing the model with the interactions terms to the model with only the main effects. Most study participants were Caucasian, precluding evaluation of potential differences by race. To evaluate the relation between a change in red meat intake with the risk of stroke, we created ‘change’ variables equal to the simple updated red meat intake (intake reported during each questionnaire year) minus the baseline red meat intake, and then included these variables, plus baseline intake, in our multivariate model. To estimate the relative risk of total stroke associated with substituting one serving/day of one major protein source for another, we fit a multivariable proportional hazards model including all the above covariates and all major protein sources entered as continuous variables (servings/day). The difference in the coefficients for two protein sources, plus their covariance, was used to estimate the relative risk and confidence interval for the substitution [7].

Results

During 2,041,679 person-years of follow-up from 1980 through 2006 in the Nurses’ Health Study, and 833,660 person-years of follow-up from 1986 through 2008 in the Health Professionals’ Follow-up Study, we documented 1,397 strokes (including 165 intraparenchymal hemorrhages, 829 ischemic strokes, 53 subarachnoid hemorrhages, and 350 of unspecified type) in men and 2,633 strokes (including 235 intraparenchymal hemorrhages, 1383 ischemic strokes, 240 subarachnoid hemorrhages, and 775 of unspecified type) in women. Characteristics of the study participants during follow-up, averaged according to proportion of person-time in each quintile of intake, are shown in Table 1. High red meat consumption was associated with a higher rate of smoking, lower physical activity, increased intake of *trans* fat, and decreased intakes of vitamin E and multivitamins in both men and women. The major groups of protein sources were not highly correlated with each other (see online-only Data Supplement at http://stroke.ahajournals.org).

In multivariable analyses adjusted for dietary and non-dietary cardiovascular disease risk factors, high intake of red meat was associated with a higher risk of total stroke (Table 2). Both processed and unprocessed red meat were significantly associated with risk; the association with processed meat was stronger in men and the association with unprocessed red meat was stronger in women but, for both foods, a test of heterogeneity by sex was not significant. Controlling for intermediate outcomes did not materially change these results (see online-only Data Supplement at http://stroke.ahajournals.org). Poultry and nut consumption were associated with a lower total stroke risk in women, and poultry consumption was associated with lower risk in the pooled analysis. We did not observe significant association between intake of fish, dairy, eggs, or legumes and risk of stroke. A trend toward reduced risk was observed with fish intake more than once per month compared to less than once per month or never (RR in men 0.85, 95% CI: 0.63 to 1.15; RR in women 0.83, 95% CI: 0.65 to 1.06). Risk seen with total processed meat, poultry excluding chicken/turkey hot dogs, whole-fat dairy excluding ice cream, and low-fat dairy excluding sherbet were similar to main findings for processed red meat, poultry, whole-fat dairy, and low-fat dairy. All findings were generally similar when ischemic and hemorrhagic strokes were separately evaluated (Table 3 and online-only Data Supplement at http://stroke.ahajournals.org). We did not observe significant effect modification of red meat intake and stroke risk by body mass index in either men or women.

We observed a significant reduction in risk of stroke among men and women who lowered their consumption of red meat intake from baseline. Compared to those with an increase of 0.6 servings/day during follow-up, men with the greatest decrease (median for quintile of change = −0.93 servings/day) had a 0.79 (95% CI: 0.62 to 0.99) risk. Compared to those with an increase of 0.3 servings/day, women with the greatest decrease (median for quintile of change = −1.16 servings/day), had a risk of 0.84 (95% CI: 0.72 to 0.99). The pooled risk for men and women was 0.83 (95% CI: 0.72 to 0.94). Results were in a similar direction when the analysis was restricted to only those participants with the highest red meat intake at baseline, although findings were not statistically significant.

In estimating the effect of substituting one protein source for another, we combined data for men and women since we did not observe significant between-study heterogeneity (Q statistic p value > 0.05 for substitutions). When compared to one serving/day of red meat, one serving/day of poultry, nuts, fish, or dairy was associated with a decreased risk of stroke (Figure). When compared to one serving/day of red meat, one serving/day of poultry was associated with a 27% (95% CI: 12% to 39%) lower risk of stroke, nuts with a 17% (95% CI: 4% to 27%) lower risk, fish with a 17% (95% CI: 0% to 30%) lower risk, low-fat dairy with an 11% (95% CI: 5% to 17%) lower risk, and whole-fat dairy with a 10% (95% CI: 4% to 16%) lower risk.

Discussion

We observed that higher consumption of red meat was associated with a higher risk of stroke; both processed and unprocessed red meat contributed to this excess incidence. Poultry intake was associated with lower risk. These associations were independent of other major protein sources, fruits, and vegetables, as well as of other stroke risk factors. Compared to red meat, intake of poultry, nuts, and both whole-fat and low-fat dairy were associated with a lower risk.

Earlier studies have found an increased risk of stroke with red meat intake, with as little as one serving per day [6, 12–13]. In a recent meta-analysis, intake of both unprocessed and processed red meat were associated with a non-significant modestly increased risk of total stroke (14% and 17%) [2]. However, only two studies had separated unprocessed from processed red meat, and the meta-analysis included a total of 1,700 cases. Our findings, with more than twice the number of cases included in the meta-analysis, are largely in agreement with earlier findings on the association between red meat and ischemic stroke. Fish intake has been associated with a lower risk of stroke in some [3–4, 14] but not all [15] studies. We did not observe a statistically significant association between fish intake and stroke risk. Poultry intake was more strongly associated with lower stroke risk than was fish intake, especially among women, for ischemic stroke, and when substituted for red meat; substituting poultry for fish was also associated with a trend toward a lower stroke risk (RR 0.89; 95% CI 0.68,1.16). Both whole-fat dairy and low-fat dairy were associated with lower stroke risk when substituted for red meat. The caloric content for a 1 oz serving of mixed nuts is 168 Kcal and for a cooked or broiled 15% fat hamburger patty is 192 Kcal [16]. Three slices of cooked, broiled, or pan-fried bacon has 129 Kcal and a cup of plain low-fat yogurt has 154 Kcal [16]. Thus, substituting nuts or yogurt for bacon at breakfast, for example, or yogurt or nuts in a salad for a hamburger at lunch or dinner could maintain energy balance.

Multiple mechanisms might mediate the relationship between protein sources and stroke risk. A diet high in protein, when compared to a diet high in carbohydrate, may lower blood pressure, a major risk factor for stroke, and improve plasma lipids [1]. Prior analyses from our group found that a lower intake of total animal protein was associated with higher risk of hemorrhagic stroke in women [17] but not in men [18]. However, this mechanism alone would not account for the different associations of various protein sources with stroke risk. A lower intake of saturated fat has been associated with a trend toward higher stroke risk in some but not all studies, [19] perhaps mediated by low total serum cholesterol levels, reduced platelet aggregation, increased vascular fragility, and increased risk for hemorrhage [17]. Such mechanisms could partly explain, for example, why dairy foods were associated with lower stroke risk. In a recent meta-analysis of prospective cohort studies, higher milk intake was associated with a nonsignificant trend toward lower stroke risk (per 200 ml/d, RR=0.87, 95% CI: 0.72, 1.05); insufficient data were available to separately evaluate low-fat versus whole-fat milk [20]. In contrast, through its effects on blood pressure, [21] sodium may account for part of the association seen between processed red meat and ischemic stroke risk. Heme iron, found in processed and unprocessed red meat, has been associated with coronary heart disease [22] and diabetes [23]. Higher intakes of potassium, magnesium, and calcium have been associated with reduced stroke risk [24]: one or more of these nutrients may help explain the reduction in risk seen when dairy products are substituted for red meat. The reasons for risk reduction seen with higher poultry intake, especially when compared to fish, are not certain, but we note that processing and cooking methods for poultry likely differ from other protein sources, as does the nutrient content, and higher poultry intake has been associated with lower risk of coronary heart disease [7]. Compared to red meat, poultry has lower amounts of heme iron and higher amounts of polyunsaturated fat.

Our analysis has important strengths and limitations. We separately examined total, hemorrhagic and ischemic stroke outcomes. We accounted for other lifestyle factors and dietary habits over time to minimize effects of time-dependent confounding. The long cohort follow-up with updated dietary data, high follow-up rate, and large number of participants provided power to detect clinically relevant differences in risks. Although we reduced measurement error in these prospective studies by the use of repeated assessment of diet, some error is inevitable. However, this error should be independent of stroke and would likely lead to an underestimate of the true associations. Misclassification of dietary covariates could create bias in unpredictable directions. The ability to control for known cardiovascular disease risk factors, assessed repeatedly during follow-up, in multivariable models reduced bias, but we cannot exclude the possibility of residual and unmeasured confounding.

Summary

In conclusion, greater red meat consumption was associated with a higher risk of stroke. Compared to the same number of servings per day of red meat, consumption of poultry, nuts, or dairy products was associated with lower risk. Similar to what we have observed for coronary heart disease [7], shifting sources of protein in the U.S. diet may contribute to the prevention of stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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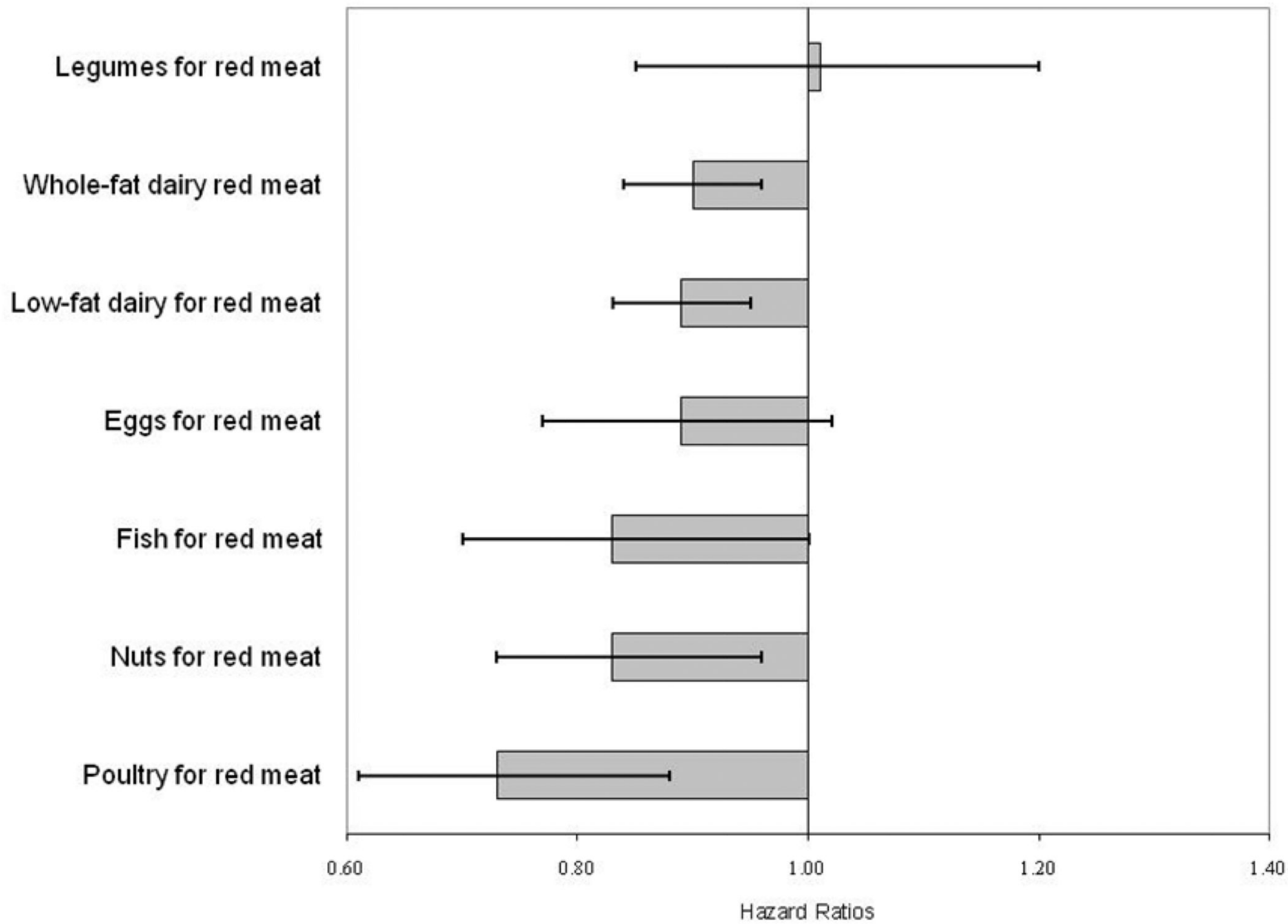

Figure. RR and 95% CI for stroke associated with substitution of dietary protein sources *

* Q statistic p value for between-study heterogeneity (null hypothesis is that *there is no* heterogeneity) for estimate of effect of substitutions > 0.05; RR and 95% CI for substitutions not shown here: poultry for fish: 0.89 (0.68,1.16); nuts for fish: 0.99 (0.80,1.23); nuts for poultry: 1.11 (0.90,1.37)

Table 2

Age-standardized characteristics, Health Professionals Follow-Up Study, 1986–2008, and Nurses' Health Study, 1980–2006 *

	Health Professionals Follow-Up Study (n=43,150)									Nurses' Health Study (n=84,010)								
	Red Meat			Poultry			Fish			Red Meat			Poultry			Fish		
Quintiles	**1st**	**3rd**	**5th**	**1st**	**3rd**	**5th**	**1st**	**3rd**	**5th**	**1st**	**3rd**	**5th**	**1st**	**3rd**	**5th**	**1st**	**3rd**	**5th**
Median intake (servings/day)	0.30	1.03	2.29	0.14	0.40	0.72	0.07	0.28	0.64	0.44	1.00	1.92	0.14	0.28	0.54	0.07	0.18	0.45
Age (yrs)	62	62	61	61	62	62	61	62	62	61	58	53	54	59	59	54	60	59
Body Mass Index (kg/m2)	25	26	27	26	26	26	26	26	26	25	26	26	25	26	27	25	26	27
Current Smoker (%)	3	6	9	9	5	3	7	6	5	13	15	22	23	16	11	21	15	13
Family History of Early MI (%)	14	11	11	10	12	14	11	12	14	19	19	18	17	19	20	17	19	20
History of:																		
High Blood Pressure (%)	32	34	34	30	34	37	32	35	35	32	34	33	30	34	37	31	34	37
High Cholesterol (%)	41	40	34	29	40	45	34	41	41	37	37	30	26	38	41	30	39	39
Current Post-Menopausal Hormone Use (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	26	27	21	19	27	28	22	28	25
Aspirin Use At Least Once Per Week (%)	36	37	30	31	37	35	33	37	35	20	21	24	24	20	20	22	18	23
Multivitamin Use (yrs)	8.5	8.5	7.7	7.4	8.3	8.8	8.3	8.7	8.1	8.2	7.4	5.9	5.8	7.6	8.4	6.1	7.9	7.9
Vitamin E Supplement Use (yes/no)	26	18	12	17	21	19	16	19	23	30	24	16	17	26	27	19	27	26
Alcohol (g/day)	9	12	13	11	12	11	10	12	12	5	6	6	6	6	6	5	6	6
Activity (METS/wk)	38	34	34	31	35	38	32	35	38	21	17	15	15	17	20	14	17	21
Calories (Kcal/day)	1685	1924	2408	1814	1972	2178	1860	1988	2107	1373	1651	2012	1521	1681	1831	1542	1695	1767

	Health Professionals Follow-Up Study (n=43,150)									Nurses' Health Study (n=84,010)								
	Red Meat			Poultry			Fish			Red Meat			Poultry			Fish		
Quintiles	1st	3rd	5th	1st	3rd	5th	1st	3rd	5th	1st	3rd	5th	1st	3rd	5th	1st	3rd	5th
Cereal Fiber (g/day)	8.1	6.3	5.0	6.3	6.6	6.5	6.2	6.5	6.7	4.4	3.8	2.9	3.5	4.0	3.9	3.5	4.1	3.9
Trans-Unsaturated Fat (g/day)	2.3	3.1	3.4	3.2	2.9	2.7	3.4	3.0	2.5	2.9	3.4	3.9	3.9	3.4	3.0	3.8	3.4	3.0

* Mean values given for continuous variables, percentages of population given for dichotomous variables, and nutrients are calorie-adjusted by the residual method

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Table 2

RR and 95% CI for total stroke by quintiles of intake of dietary protein sources among 43,150 US men and 84,010 US women*,†

		Quintiles						
		1st	2nd	3rd	4th	5th	P for trend	RR for 1 serving/day
Total red meat								
Men	Servings/day	0.30	0.68	1.03	1.46	2.29		
	Multivariable RR	1.00	0.98 (0.81,1.18)	1.08 (0.89,1.32)	1.24 (1.01,1.52)	1.28 (1.02,1.61)	0.01	1.15 (1.03,1.27)
Women	Servings/day	0.44	0.74	1.00	1.32	1.92		
	Multivariable model	1.00	1.12 (0.99,1.26)	1.11 (0.97,1.27)	1.17 (1.01,1.36)	1.19 (1.00,1.41)	0.07	1.11 (0.99,1.24)
Pooled	Multivariable model	1.00	1.08 (0.97,1.19)	1.10 (0.99,1.23)	1.19 (1.06,1.34)	1.22 (1.07,1.40)	<0.01	1.13 (1.04,1.22)
Processed Red Meat								
Men	Servings/day	0.03	0.14	0.21	0.39	0.71		
	Multivariable model	1.00	1.01 (0.84,1.21)	0.91 (0.75,1.10)	1.12 (0.92,1.36)	1.27 (1.03,1.55)	<0.01	1.53 (1.16,2.01)
Women	Servings/day	0.05	0.14	0.23	0.35	0.64		
	Multivariable model	1.00	0.98 (0.87,1.11)	1.06 (0.93,1.21)	1.09 (0.95,1.24)	1.10 (0.95,1.27)	0.13	1.19 (0.95,1.50)
Pooled	Multivariable model	1.00	0.99 (0.89,1.10)	1.01 (0.91,1.13)	1.10 (0.98,1.22)	1.15 (1.02,1.30)	<0.01	1.32 (1.11,1.57)
Unprocessed Red Meat								
Men	Servings/day	0.14	0.35	0.53	0.71	1.11		
	Multivariable model	1.00	1.10 (0.91,1.32)	1.06 (0.87,1.29)	1.23 (1.00,1.51)	1.11 (0.88,1.39)	0.51	1.08 (0.86,1.34)
Women	Servings/day	0.28	0.43	0.60	0.78	1.08		
	Multivariable model	1.00	1.09 (0.96,1.23)	1.04 (0.91,1.19)	1.13 (0.98,1.30)	1.19 (1.02,1.40)	0.04	1.22 (1.01,1.47)
Pooled	Multivariable model	1.00	1.09 (0.98,1.21)	1.05 (0.94,1.17)	1.16 (1.03,1.31)	1.16 (1.02,1.33)	0.05	1.16 (1.00,1.33)
Poultry								

		Quintiles						
		1st	2nd	3rd	4th	5th	P for trend	RR for 1 serving/day
Men	Servings/day	0.14	0.25	0.40	0.50	0.72		
	Multivariable model	1.00	1.01 (0.85,1.20)	1.00 (0.84,1.18)	1.06 (0.87,1.28)	0.97 (0.81,1.17)	0.74	0.95 (0.70,1.28)
Women	Servings/day	0.14	0.19	0.28	0.40	0.54		
	Multivariable model	1.00	1.01 (0.88,1.15)	0.91 (0.80,1.03)	0.91 (0.80,1.04)	0.82 (0.71,0.94)	<0.01	0.61 (0.45,0.83)
Pooled	Multivariable model	1.00	1.01 (0.91,1.12)	0.94 (0.85,1.04)	0.96 (0.86,1.07)	0.87 (0.78,0.97)	0.02	0.77 (0.62,0.95)
Fish								
Men	Servings/day	0.07	0.18	0.28	0.39	0.64		
	Multivariable model	1.00	1.10 (0.92,1.30)	0.94 (0.78,1.14)	1.00 (0.83,1.20)	1.03 (0.84,1.25)	0.92	0.98 (0.72,1.35)
Women	Servings/day	0.07	0.14	0.18	0.28	0.45		
	Multivariable model	1.00	0.91 (0.80,1.03)	0.93 (0.82,1.06)	0.98 (0.86,1.12)	0.87 (0.75,1.01)	0.18	0.79 (0.55,1.12)
Pooled	Multivariable model	1.00	0.97 (0.88,1.08)	0.93 (0.84,1.04)	0.99 (0.89,1.10)	0.92 (0.82,1.04)	0.33	0.89 (0.71,1.13)
Whole-fat dairy								
Men	Servings/day	0.21	0.55	0.86	1.32	2.55		
	Multivariable model	1.00	0.85 (0.71,1.01)	0.84 (0.70,1.01)	0.92 (0.77,1.11)	0.87 (0.72,1.06)	0.46	0.97 (0.90,1.05)
Women	Servings/day	0.34	0.65	1.00	1.52	2.81		
	Multivariable model	1.00	0.94 (0.84,1.06)	0.95 (0.84,1.07)	0.88 (0.77,1.00)	0.90 (0.79,1.03)	0.15	0.96 (0.91,1.01)
Pooled	Multivariable model	1.00	0.91 (0.83,1.01)	0.91 (0.82,1.01)	0.89 (0.80,0.99)	0.89 (0.80,1.00)	0.11	0.97 (0.93,1.01)
Low-fat dairy								
Men	Servings/day	0.11	0.47	0.89	1.38	2.64		
	Multivariable model	1.00	0.87 (0.72,1.03)	0.92 (0.77,1.10)	0.91 (0.76,1.08)	0.94 (0.78,1.12)	0.80	0.99 (0.93,1.06)
Women	Servings/day	0.07	0.43	0.79	1.20	2.20		
	Multivariable model	1.00	0.95 (0.84,1.08)	0.94 (0.82,1.07)	0.96 (0.84,1.10)	0.91 (0.79,1.04)	0.24	0.96 (0.91,1.03)

			Quintiles					
		1st	2nd	3rd	4th	5th	P for trend	RR for 1 serving/day
Pooled	Multivariable model	1.00	0.92 (0.83,1.02)	0.93 (0.84,1.04)	0.94 (0.85,1.05)	0.92 (0.82,1.03)	0.30	0.98 (0.93,1.02)
Eggs								
Men	Servings/day	0.02	0.07	0.17	0.43	0.79		
	Multivariable model	1.00	0.80 (0.66,0.97)	0.88 (0.73,1.05)	0.80 (0.66,0.96)	0.84 (0.68,1.04)	0.29	0.88 (0.69,1.11)
Women	Servings/day	0.07	0.18	0.31	0.43	0.67		
	Multivariable model	1.00	0.90 (0.80,1.01)	0.94 (0.83,1.05)	0.86 (0.76,0.99)	0.91 (0.80,1.04)	0.19	0.87 (0.70,1.07)
Pooled	Multivariable model	1.00	0.87 (0.79,0.96)	0.92 (0.83,1.01)	0.84 (0.75,0.93)	0.89 (0.80,1.00)	0.09	0.87 (0.75,1.02)
Nuts								
Men	Servings/day	0.00	0.07	0.14	0.25	0.60		
	Multivariable model	1.00	0.94 (0.79,1.12)	0.95 (0.80,1.13)	1.01 (0.86,1.20)	0.92 (0.77,1.09)	0.39	0.89 (0.68,1.16)
Women	Servings/day	0.00	0.04	0.07	0.12	0.34		
	Multivariable model	1.00	0.94 (0.83,1.06)	0.91 (0.80,1.04)	0.97 (0.85,1.10)	0.86 (0.75,0.98)	0.05	0.71 (0.51,1.00)
Pooled	Multivariable model	1.00	0.94 (0.85,1.04)	0.93 (0.83,1.03)	0.99 (0.89,1.09)	0.88 (0.79,0.98)	0.06	0.82 (0.66,1.01)
Legumes								
Men	Servings/day	0.07	0.14	0.21	0.32	0.57		
	Multivariable model	1.00	1.03 (0.86,1.23)	1.06 (0.89,1.26)	1.04 (0.87,1.24)	1.07 (0.89,1.29)	0.48	1.13 (0.81,1.58)
Women	Servings/day	0.07	0.14	0.17	0.24	0.43		
	Multivariable model	1.00	0.99 (0.87,1.13)	1.19 (1.04,1.36)	1.05 (0.92,1.19)	1.06 (0.93,1.22)	0.64	1.09 (0.77,1.53)
Pooled	Multivariable model	1.00	1.01 (0.91,1.12)	1.14 (1.03,1.27)	1.05 (0.94,1.16)	1.06 (0.95,1.19)	0.41	1.11 (0.87,1.41)

[*] Median values shown for quintiles of servings/day

[†] Multivariable model stratified on age (months) and time period (13 periods in NHS, 11 in HPFS) and includes: body mass index (10 categories), cigarette smoking (never, past, current 1–14 cig/day, current 14–25 cig/day, current 25+ cig/day), physical exercise (<3, 3–9, 9–18,18–27, 27+ metabolic equivalents/week), parental history of early myocardial infarction (before age 60), menopausal status in women (pre-menopausal, postmenopausal with no history of hormone replacement, postmenopausal with history of hormone replacement, postmenopausal with current hormone replacement), multivitamin

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use (quintiles of yrs), vitamin E supplement use (yes/no), aspirin use at least once per week (yes/no), total energy (quintiles of Kcal), cereal fiber (quintiles of g/day), alcohol (quintiles of g/day), trans-fat (quintiles of g/day), fruit and vegetables (quintiles of servings/day), and other protein sources (quintiles of servings/day)

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Table 3

Pooled RR and 95% CI for stroke subtypes by quintiles of intake of dietary protein sources among 43,150 US men and 84,010 US women *

		Quintiles						
		1st	**2nd**	**3rd**	**4th**	**5th**	**P for trend**	**RR for 1 serving/day**
Total Red Meat								
	Hemorrhagic	1.00	1.28 (0.92,1.77)	1.24 (0.87,1.76)	1.36 (0.93,1.99)	1.19 (0.77,1.86)	0.44	1.10 (0.87,1.39)
	Ischemic	1.00	1.07 (0.93,1.23)	1.09 (0.94,1.27)	1.18 (1.00,1.38)	1.22 (1.01,1.47)	0.03	1.12 (1.01,1.24)
Processed Red Meat								
	Hemorrhagic	1.00	1.06 (0.76,1.47)	1.08 (0.76,1.53)	1.40 (0.99,1.96)	1.13 (0.76,1.67)	0.25	1.39 (0.80,2.41)
	Ischemic	1.00	1.01 (0.88,1.16)	0.99 (0.86,1.15)	1.02 (0.88,1.19)	1.15 (0.98,1.35)	0.03	1.30 (1.02,1.64)
Unprocessed Red Meat								
	Hemorrhagic	1.00	0.95 (0.69,1.31)	1.00 (0.71,1.41)	1.04 (0.72,1.50)	0.83 (0.55,1.27)	0.57	0.88 (0.56,1.37)
	Ischemic	1.00	1.22 (1.06,1.41)	1.15 (0.99,1.34)	1.27 (1.08,1.49)	1.27 (1.06,1.53)	0.05	1.21 (1.00,1.47)
Poultry								
	Hemorrhagic	1.00	0.79 (0.57,1.11)	0.89 (0.66,1.22)	0.79 (0.55,1.12)	0.74 (0.52,1.06)	0.14	0.60 (0.30,1.18)
	Ischemic	1.00	1.01 (0.88,1.17)	0.90 (0.79,1.03)	0.99 (0.85,1.15)	0.89 (0.76,1.03)	0.21	0.83 (0.62,1.11)
Fish								
	Hemorrhagic	1.00	0.80 (0.58,1.09)	0.71 (0.51,1.00)	0.71 (0.50,1.00)	0.79 (0.55,1.12)	0.38	0.72 (0.34,1.50)
	Ischemic	1.00	0.98 (0.85,1.13)	0.95 (0.82,1.11)	1.02 (0.88,1.19)	0.94 (0.81,1.11)	0.66	0.93 (0.68,1.28)
Whole-fat dairy								
	Hemorrhagic	1.00	0.75 (0.54,1.03)	0.85 (0.61,1.18)	0.78 (0.56,1.09)	0.98 (0.69,1.37)	0.37	1.06 (0.93,1.21)
	Ischemic	1.00	0.90 (0.79,1.03)	0.87 (0.76,1.00)	0.88 (0.76,1.02)	0.87 (0.75,1.02)	0.18	0.96 (0.91,1.02)
Low-fat dairy								
	Hemorrhagic	1.00	0.77 (0.56,1.07)	0.80 (0.58,1.12)	0.79 (0.56,1.10)	0.88 (0.62,1.24)	0.99	1.00 (0.87,1.15)
	Ischemic	1.00	0.92 (0.79,1.06)	0.98 (0.85,1.13)	0.94 (0.81,1.09)	0.94 (0.81,1.10)	0.56	0.98 (0.92,1.04)
Eggs								
	Hemorrhagic	1.00	1.09 (0.79,1.51)	1.40 (1.01,1.93)	1.16 (0.81,1.64)	0.70 (0.46,1.06)	0.03	0.56 (0.33,0.93)
	Ischemic	1.00	0.84 (0.73,0.96)	0.86 (0.75,0.98)	0.80 (0.69,0.93)	0.90 (0.77,1.04)	0.36	0.91 (0.73,1.12)
Nuts								

		Quintiles						
		1st	2nd	3rd	4th	5th	P for trend	RR for 1 serving/day
	Hemorrhagic	1.00	1.04 (0.76,1.43)	0.81 (0.57,1.13)	0.86 (0.62,1.20)	0.83 (0.59,1.16)	0.21	0.66 (0.34,1.26)
	Ischemic	1.00	0.97 (0.84,1.11)	1.00 (0.86,1.15)	1.03 (0.89,1.18)	0.97 (0.84,1.12)	0.59	0.93 (0.70,1.22)
Legumes								
	Hemorrhagic	1.00	0.82 (0.58,1.15)	1.26 (0.91,1.74)	0.93 (0.67,1.30)	1.15 (0.82,1.62)	0.32	1.46 (0.69,3.06)
	Ischemic	1.00	0.96 (0.83,1.11)	1.03 (0.89,1.20)	1.04 (0.90,1.20)	1.14 (0.98,1.32)	0.02	1.45 (1.06,2.00)

* Pooled multivariable models are stratified on age (months) and time period (13 periods in NHS, 11 in HPFS) and include: body mass index (10 categories), cigarette smoking (never, past, current 1–14 cig/day, current 14–25 cig/day, current 25+ cig/day), physical exercise (<3, 3–9, 9–18, 18–27, 27+ metabolic equivalents/week), parental history of early myocardial infarction (before age 60), menopausal status in women (pre-menopausal, postmenopausal with no history of hormone replacement, postmenopausal with history of hormone replacement, postmenopausal with current hormone replacement), multivitamin use (quintiles of yrs), vitamin E supplement use (yes/no), aspirin use at least once per week (yes/no), total energy (quintiles of Kcal), cereal fiber (quintiles of g/day), alcohol (quintiles of g/day), trans-fat (quintiles of g/day), fruit and vegetables (quintiles of servings/day), and other protein sources (quintiles of servings/day)