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Nut Consumption and Risk of Stroke in US Male Physicians

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Abstract

Background and Aims—While nut consumption has been shown to lower the risk of hypertension and coronary disease, it is not known whether nut consumption is associated with the risk of stroke. We sought to examine whether nut consumption is associated with total and subtypes of stroke.

Methods—Prospective cohort of 21,078 participants from the Physicians' Health Study (1982–2008) who were free of stroke at baseline. Nut consumption was assessed using a simple 19-item food questionnaire and stroke cases were confirmed after reviewing medical records. We used Cox proportional hazards regression to estimate relative risks of total, ischemic, and hemorrhagic stroke according to consumption of any nuts.

Results—During a mean follow up of 21.1 years, 1,424 incident cases of stroke occurred (219 hemorrhagic, 1,189 ischemic, and 16 of undetermined cause). There was no statistically significant association between nut consumption and total or ischemic stroke. In contrast, there was a suggestive non-linear relation between nut intake and hemorrhagic stroke: compared to subjects who did not consume nuts, multivariable adjusted hazard ratios (95% CI) for hemorrhagic stroke for subjects consuming nuts < 1, 1–4, 5–6, and ≥ 7 times/week were 1.13 (0.78–1.62), 1.05 (0.70–1.58), 0.49 (0.27–0.89), 1.50 (0.79–2.84), and 1.84 (0.95–3.57), respectively (p for quadratic trend 0.12).

Conclusions—Our data showed no association between nuts and ischemic stroke and suggested a J-shaped relation between nut consumption and hemorrhagic stroke. Replication of our findings in the general population is warranted.

Keywords

Diet; stroke; epidemiology; nuts; nutrition

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Conflict of interest:

None to disclose.

Introduction

Despite a decline in the rate of stroke in the US^{1,2}, it remains a major public health issue and is associated with disability, mortality, and major direct and indirect costs^{3,4}. This underscores the importance of prevention strategies aiming at reducing the incidence of stroke given the limited acute treatment options. Hypertension is a major risk factor for stroke⁵ and can be influenced by modifiable lifestyle factors including diet. Among dietary factors, nuts are important source of macro- and micronutrients with health benefits⁶ as they are low in sodium and also contain a variety of nutrients including unsaturated fatty acids, and minerals such as magnesium and potassium. Previous studies have suggested that nuts may have beneficial effects on blood pressure⁷⁻⁹, lipids^{10,11}, and insulin sensitivity¹². In a feeding trial, a Mediterranean diet enriched with 30 g/d of nuts (walnuts –15 g/d, hazelnuts –7.5 g/d, and almonds –7.5 g/d) was associated with reduced blood pressure compared to low-fat diet¹³. We have previously reported an inverse relation between nut intake and hypertension in male physicians¹⁴. It is thus possible that these physiologic effects of nuts may confer a lower risk of stroke among people who consume them on a regular basis. However, there is a lack of data on the relation between nut consumption and the risk of total stroke or stroke subtypes. Since omega-3 fatty acids contained in nuts have been shown to inhibit platelet aggregation^{15,16}, it is possible that nut consumption may prevent or attenuate the progression of thrombo-embolic events. The current study sought to prospectively examine whether nut consumption is associated with the risk of total stroke and stroke subtypes.

Materials and Methods

Study population

Participants in this project were drawn from the Physicians' Health Study (PHS), which is a completed randomized, double-blind, placebo-controlled trial designed to study low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer. A detailed description of the PHS has been published previously¹⁷. Each participant gave written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol. Of the total 22,071 participants, we excluded 615 subjects because of missing data on nut consumption, 22 subjects who reported stroke diagnosis prior to receiving the 12 months post-randomization when nut consumption was assessed, 3 cases of unrefuted stroke, 353 people with missing covariates (body mass index, smoking, breakfast cereal, alcohol intake, fruit and vegetable consumption, or exercise). Thus, a final sample of 21,078 subjects was used for current analyses.

Assessment of nut consumption

Information on nut consumption was self-reported using a 19-item semi-quantitative food frequency questionnaire administered 12 months post-randomization (1983–1985). Participants were asked to indicate “how often, on average, they have eaten nuts (small packet or 1 oz.)”. Possible response categories included “rarely/never”, “1–3/month”, “1/week”, “2–4/week”, “5–6/week”, “daily”, and “2+/day”. Due to limited number of participants in each of the last 2 highest categories, we combined any nut consumption of “daily” and “2+/d” to obtain stable estimates (subsequently referred to as ≥ 7 /week). Although the food frequency questionnaire was not validated in the PHS I, it has been validated in several cohorts^{18,19}. While the questionnaire asked about peanut butter use, no data were collected on the specific type of nuts consumed.

Ascertainment of stroke

Detailed description of ascertainment of stroke in the PHS has been published previously²⁰. Briefly, information of incident stroke was collected through yearly follow-up questionnaires.

For subjects who reported stroke on a follow-up questionnaire, we asked permission to obtain their medical records. An end points committee confirmed a diagnosis of a stroke after review of medical records. Non-fatal stroke was defined as a focal neurological deficit of sudden or rapid onset lasting more than 24 hours and was classified according to criteria established by the National Survey of Stroke²¹ into ischemic, hemorrhagic (including intraparenchymal and subarachnoid hemorrhage), and unknown subtypes, using available information in the medical records including brain imaging²². Fatal strokes were confirmed by review of autopsy reports, death certificates, medical records, or information from the next of kin or family members.

Other variables

Demographic data were collected at baseline. At 12 months post-randomization (when nut consumption was assessed), information on prevalent angina pectoris, myocardial infarction, coronary angioplasty and revascularization, atrial fibrillation, type 2 diabetes, and hypertension was collected. Hypertension was defined as systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg, treatment for hypertension, or spontaneous self-reports of hypertension. Data on selected foods such as fruits and vegetables, breakfast cereal; physical activity; smoking; alcohol consumption; liver intake; and low fat and whole milk were obtained through self-reports at baseline. For subjects with missing information on breakfast cereal at baseline, we used breakfast cereal information collected at 24 months. Additional information on selected foods including fish, red meat, ice cream, cheese, chicken, and turkey was collected. We assigned the mid-point of the response category as outlined for nuts above to each response category and summed up subcategories within each food group (i.e. low fat milk, yogurt, and cheese for dairy; dark meat fish, tuna, shrimp, and other fish for fish; and beef, pork, lamb, and hotdogs for red meat). For “2+/day” category, we assigned a value of 14 times per week.

Statistical analyses

We classified each subject into one of the following categories of nut consumption: 0, < 1, 1, 2–4, 5–6, and ≥ 7 times per week. We computed person-time of follow up from exposure assessment (12 months post-randomization) until the first occurrence of a) stroke, b) death, or c) date of receipt of last follow-up questionnaire (March 2008). For each category of nut consumption, incidence rate was computed by dividing the number of cases by the corresponding person-time of follow up. We used Cox proportional hazards models to compute multivariable-adjusted hazard ratios with corresponding 95% confidence intervals using subjects reporting no nut consumption as the reference group. We assessed confounding smoking, alcohol intake, hypertension, aspirin assignment, diabetes, body mass index, regular exercise, and consumption of breakfast cereal, dairy products, fruits and vegetables, fish, and red meat using the 10% change in estimate of effect²³. The fully adjusted model controlled for age, body mass index (<25, 25–29, 30 kg/m²), smoking (never, former, current smoker), aspirin arm (yes/no), fruit and vegetable intake (<3, 3–4, 5–6, 7–13, 14+ servings per week), alcohol consumption (<1, 1–4, 5–7, and 8+ drinks/week), breakfast cereal (0, ≤ 1 , 2–6, and 7+/week), red meat (quintiles), fish (up to 1, 2, 3, and 4+ servings/week), dairy (quintiles), exercise (2+/week vs. ≤ 1 per week), and prevalent hypertension, diabetes, atrial fibrillation, and coronary heart disease (angina pectoris, myocardial infarction, coronary bypass or angioplasty). We analyzed total stroke, ischemic stroke, and hemorrhagic stroke separately. Assumptions for proportional hazard models were tested (by including main effects and product terms of covariates and logarithmic transformed time factor) and were met (all p values >0.05). We also conducted sensitivity analyses excluding subjects with follow-up time of less than 2 years (n=235) to allow sufficient window between exposure and outcome. Furthermore, we repeated analyses with follow-up time restricted to 5 and 10 years with the rationale that within a shorter period of time, individuals are less likely to change their frequency of nut consumption. All

analyses were completed using SAS, version 9.1 (SAS Institute, NC). Significance level was set at $\alpha=0.05$, two-tailed *p* values.

Results

Table 1 presents the crude baseline characteristics of 21,078 study participants according to categories of nut consumption. The mean age was 54.6 ± 9.5 years (range 40.7 to 86.7). Higher consumption of nuts was associated with a lower prevalence of diabetes and atrial fibrillation, and a higher proportion of fruit and vegetable, fish, dairy, and breakfast cereal consumption. During the follow up, 1,424 new cases of stroke occurred (1,189 ischemic, 219 hemorrhagic, and 16 of undetermined cause). Table 2 provides characteristics of subjects with stroke and those without stroke. In a crude analysis, there was a non-linear inverse relation between nut consumption and total stroke (*p* for quadratic trend 0.001, Table 3). However, adjustment for potential confounders in a multivariable model completely eliminated this association (Table 3). There was no evidence for an association between nut consumption and ischemic stroke after adjustment for potential confounders (Table 3). In contrast, there was a suggestive J-shaped relation between nut intake and hemorrhagic stroke with the lowest hazard ratio among people consuming 2–4 times /week (HR: 0.49; 95% CI: 0.27–0.89) and the highest hazard ratio in subjects consuming 7 or more servings of nuts per week [HR (95% CI): 1.84 (0.95–3.57)], *P* for quadratic trend 0.10, Table 3. Exclusion of subjects with follow up time below 2 years did not appreciably alter the results (data not shown). Furthermore, restriction of follow up to 5 or 10 years did not alter the findings (data not shown).

Discussion

In this large prospective cohort of apparently healthy men at baseline, we found no evidence for an association between nut consumption and the risk of total or ischemic stroke after an average follow up of 21.1 years. For hemorrhagic stroke, we observed suggestive evidence for a J-shaped relation with nut consumption. Despite advances in medical and surgical treatment, stroke is still associated with major disability and is the 3rd leading cause of death. This underscores the importance of preventive measures for this disease. Several dietary factors have shown beneficial effects on stroke predictors. Data from the PREDIMED trial showed that compared with a low-fat diet, Mediterranean diets supplemented with 30 g/d of nuts (almonds, hazelnuts, and walnuts) and olive oil were associated with 7.1 and 5.9 mm Hg reduction in systolic blood pressure after 3 months of intervention, respectively, among ~257 adult men and women per intervention group¹³. In that study, corresponding effects for diastolic blood pressure were 2.6 and 1.6 mm Hg for Mediterranean diet with nuts and olive oil¹³, respectively. Nut consumption may lower the risk of stroke via its beneficial effects on blood pressure or other predictors of stroke. Nut consumption has been associated with improved lipid profile^{24–28}, insulin sensitivity^{12,29}, and reduced inflammation^{6,13,30}. However, our data on total and ischemic stroke do not support this hypothesis.

The J-shaped relation observed between nut consumption and hemorrhagic stroke merits some comments. We had limited number of stroke in the higher categories of nut consumption. Consequently our data should be interpreted with caution. However, it is possible that omega-3 fatty acids contained in nuts may be partially responsible for the observed increased risk of hemorrhagic stroke with consumption of nuts 5 or more times per week. Previous studies have demonstrated that polyunsaturated fatty acids found in nuts may inhibit platelet aggregation^{15,16}. This may increase the propensity to bleeding. In a necropsy study in Greenland, the concentration of total n-3 polyunsaturated fatty acids in perirenal adipose tissue was higher (2.3 units) in 4 cases of fatal hemorrhagic stroke than in 26 subjects without cerebral pathology (1.5 units)³¹. In contrast, the Cardiovascular Health Study³² and the Health Professional Follow-up Study³³ did not find a statistically significant association between fish intake and

hemorrhagic stroke. Of note is that n-3 fatty acids only affect bleeding times at higher concentrations (3–15 g/d)^{34,35}. The lower intake of fish in the Western diet compared with Greenland Inuit may partially account for the inconsistency in these findings. Lastly, it is possible that people with a lifestyle considered healthy for ischemic stroke may be at increased risk for hemorrhagic stroke³⁶. For example, subjects with low body mass index and low LDL-cholesterol have been reported to have a higher risk of hemorrhagic stroke³⁷.

Strengths of the present paper are the large sample size, large number of outcomes events, the long duration of follow up, and the ascertainment of stroke through review of medical records. However, our study has some limitations. While the number of stroke events is large, the number of stroke subtypes according to nut consumption categories is relatively small. Thus, the statistically significant results for hemorrhagic stroke should be interpreted with caution. The generalizability of our findings is limited by the fact that all participants were male physicians who may have different behaviors or lifestyle habits than the general population. Nut consumption was assessed only once (12 months post-randomization) and since subjects may have changed their dietary habits, we were not able to account for such changes in our analyses. Such misclassification may bias the results towards the null and may partially explain the lack of an association between nuts and ischemic stroke in this study. However, the fact that we have shown an inverse relation between nuts assessed at one single time point and incident hypertension¹⁴ in the same cohort does not support the hypothesis of a large misclassification of nuts over time in this population. In addition, our findings on ischemic stroke did not change when we restricted the follow-up time to 5 or 10 years (a period within which one could assume little change in nut consumption). Since we used a simple questionnaire to assess nut consumption, we were unable to adjust for total energy intake and other nutrients consumed by study subjects. In addition, we did not have data on types of nuts consumed; their preparation including salted, spiced, roasted, or raw nuts to examine the influence of types of nuts or preparation method on the risk of total stroke and stroke subtype. The prevalence of atrial fibrillation was higher in stroke cases than in non-cases, suggesting that the use of warfarin might have been more prevalent in people with stroke. Such use of anticoagulant may have confounded the association between nut consumption and hemorrhagic stroke. Although we did not have information on warfarin use for further evaluation, we did adjust for atrial fibrillation (more likely to be correlated with warfarin use during follow up). Lastly, given the observational design of the present study, we can not exclude unmeasured or residual confounding as a possible explanation for observed findings.

In conclusion, our data suggest no association between nut consumption and total or ischemic stroke. However, there is suggestive J-shaped relation between nut consumption and hemorrhagic stroke. Since we had limited number of hemorrhagic strokes in the highest categories of nut consumption, replication of our findings in other populations along with assessment of types of nuts consumed and underlying physiologic mechanisms are warranted.

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Table 1

Baseline characteristics of 21,078 US male physicians according to nut consumption

Characteristics	Nut intake (servings/week)					
	0 (N=4,260)	<1 (N=7,658)	1 (N=4,984)	2-4 (N=2,846)	5-6 (N=776)	≥7 (N=554)
Age (y) *	55.4±9.8	54.3±9.4	54.3±9.3	54.4±9.3	55.0±9.5	56.1±9.8
Body mass index (kg/m ²) *	24.8±2.9	24.8±2.8	24.9±2.8	24.7±2.6	24.6±2.7	24.1±2.5
Fruits & vegetables (serving/d) †	2.4 (1.4-2.9)	2.4 (1.4-2.9)	2.2 (1.4-2.9)	2.3 (1.6-3.0)	2.3 (1.6-3.1)	2.4 (1.6-3.3)
Fish (servings/week) †	2.0 (1.0-3.0)	2.0 (1.5-3.0)	2.0 (1.5-3.0)	2.0 (1.5-3.5)	2.0 (1.5-4.0)	2.0 (1.5-3.5)
Dairy (servings/week) †	4.0 (1.0-7.5)	4.0 (1.5-8.0)	5.0 (2.0-8.0)	6.0 (2.0-8.5)	6.0 (2.5-10.0)	6.5 (1.5-10.0)
Red meat (servings/week) †	4.5 (2.5-7.0)	5.0 (3.0-7.0)	6.0 (3.5-7.0)	5.5 (3.5-7.0)	5.5 (3.0-7.0)	4.8 (3.0-7.0)
Breakfast cereal intake (%)	64.7	71.0	75.4	75.8	72.4	74.2
Aspirin arm (%)	50.4	49.9	49.2	50.3	51.8	51.4
Diabetes mellitus (%)	3.6	2.9	2.9	3.4	3.6	5.8
Hypertension (%)	26.7	24.4	23.5	22.4	20.8	19.1
Atrial fibrillation (%)	1.6	1.7	2.0	1.5	2.5	2.7
Coronary heart disease (%)	3.0	2.4	2.0	2.4	2.8	2.9
Current drinkers (%)	83.3	86.0	86.1	85.1	84.4	81.0
Exercise (%)	67.4	71.9	74.6	75.3	75.0	77.3
Current smokers (%)	12.4	10.8	10.5	10.8	9.0	11.6

* Mean ± standard deviation

† Median (interquartile range)

Table 2

Baseline characteristics of 21,078 US male physicians according to incident stroke

Characteristics	Stroke cases (N=1,424)	Non-cases (N=19,654)	P
Follow-up time (y)	11.9±6.3	21.7±5.2	<0.0001
Age (y)*	61.6±9.2	54.1±9.3	<0.0001
Body mass index (kg/m ²)*	25.2±2.8	24.7±2.8	<0.0001
Fruits & vegetables (serving/d) [†]	2.3 (1.6–3.1)	2.1 (1.5–2.9)	0.0001
Fish (servings/week) [†]	2.0 (1.5–3.0)	2.0 (1.5–3.0)	0.12
Dairy (servings/week) [†]	6.0 (1.5–8.0)	4.5 (1.5–8.0)	0.005
Red meat (servings/week) [†]	5.0 (3.5–7.0)	5.0 (3.5–7.0)	0.11
Breakfast cereal intake (%)	72.4	71.5	0.73
Aspirin arm (%)	48.9	50.1	0.39
Diabetes mellitus (%)	8.3	2.8	<0.0001
Hypertension (%)	42.6	22.8	<0.0001
Atrial fibrillation (%)	3.4	1.7	<0.0001
Coronary heart disease (%)	5.0	2.3	<0.0001
Current drinkers (%)	84.3	85.2	<0.0001
Exercise (%)	69.0	72.6	0.004
Current smokers (%)	13.8	10.8	0.0001

* Mean ± standard deviation

[†] Median (interquartile range); P values were obtained using Chi-squared for categorical variables and t-test for continuous variables.

Table 3

Hazard ratios (95% CI) for hemorrhagic, ischemic, and total stroke according to nut consumption

	Nut consumption (times per week)						P for trend [†]
	0	<1	1	2-4	5-6	≥7	
Total stroke							
Cases	320	480	334	181	63	46	
Crude	1.0	0.81 (0.70-0.93)	0.86 (0.74-1.00)	0.81 (0.68-0.97)	1.04 (0.80-1.37)	1.10 (0.81-1.50)	0.001
Adjusted model *	1.0	0.91 (0.79-1.05)	0.95 (0.81-1.11)	0.90 (0.75-1.08)	1.11 (0.85-1.46)	1.07 (0.79-1.46)	0.12
Ischemic stroke							
Cases	271	387	280	166	51	34	
Crude	1.0	0.77 (0.66-0.90)	0.85 (0.72-1.01)	0.88 (0.72-1.06)	1.00 (0.74-1.34)	0.96 (0.67-1.37)	0.01
Adjusted model *	1.0	0.86 (0.74-1.01)	0.94 (0.79-1.11)	0.97 (0.80-1.18)	1.06 (0.79-1.43)	0.93 (0.65-1.34)	0.30
Hemorrhagic stroke							
Cases	46	84	52	14	12	11	
Crude	1.0	0.99 (0.69-1.41)	0.93 (0.63-1.39)	0.44 (0.24-0.79)	1.38 (0.73-2.61)	1.83 (0.95-3.53)	0.02
Adjusted model *	1.0	1.13 (0.78-1.62)	1.05 (0.70-1.58)	0.49 (0.27-0.89)	1.50 (0.79-2.84)	1.84 (0.95-3.57)	0.12

* Adjusted for age, aspirin assignment, body mass index (<25, 25-29, 30 kg/m²), alcohol consumption (<1, 1-4, 5-7, and 8+ drinks/week), smoking (never, former, current smoker), fruit and vegetable intake (<3, 3-4, 5-6, 7-13, 14+ servings/week), regular exercise (yes/no), breakfast cereal (0, ≤ 1, 2-6, and 7+/week), red meat (quintiles), fish (up to 1, 2, 3, and 4+ servings/week), dairy consumption (quintiles), and prevalent hypertension (yes/no), diabetes, atrial fibrillation, coronary heart disease.

[†] P value for quadratic trend.