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Coffee consumption and risk of stroke in women

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Abstract

Background—Data on the association between coffee consumption and risk of stroke are sparse. We assessed the association between coffee consumption and the risk of stroke over 24 years of follow-up in women.

Methods and Results—We analyzed data from a prospective cohort of 83,076 women in the Nurses' Health Study without history of stroke, coronary heart disease, diabetes, or cancer at baseline. Coffee consumption was first assessed in 1980, and then repeatedly every 2-4 years; with follow-up through 2004. We documented 2280 strokes of which 426 were hemorrhagic strokes, 1224 ischemic strokes, and 630 undetermined. In multivariable Cox regression models with adjustment for age, smoking status, body mass index, physical activity, alcohol intake, menopausal status, hormone replacement therapy, aspirin use, and dietary factors, the relative risks (RRs) of stroke across categories of coffee consumption (<1 cup/mo, 1/mo-4/wk, 5-7/wk, 2-3/d, and ≥4/d) were: 1, 0.98 (95% confidence interval [CI] 0.84-1.15), 0.88 (0.77-1.02), 0.81 (0.70-0.95), and 0.80 (0.64-0.98); p for trend= 0.003. After further adjustment for high blood pressure, hypercholesterolemia, and type 2 diabetes the inverse association remained significant. The association was stronger among never and past smokers [RR (95% CI) for ≥4 cups/d vs. <1 cup/mo: 0.57 (0.39-0.84)] than among current smokers [RR (95% CI) for ≥4 cups/d vs. <1 cup/mo: 0.97 (0.63-1.48)]. Other drinks containing caffeine, such as tea and caffeinated soft drinks, were not associated with stroke. Decaffeinated coffee was associated with a trend towards lower risk of stroke after adjustment for caffeinated coffee consumption [RR (95% CI) for 2 or more cups/d vs. <1 cup/mo: 0.89 (0.73-1.08); p for trend= 0.05].

Conclusions—Long-term coffee consumption was not associated with an increased risk of stroke in women. In contrast, our data suggest that coffee consumption may modestly reduce risk of stroke.

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Keywords

coffee; stroke; Nurses' Health Study; women

Recent analyses support the hypothesis that coffee consumption does not increase the risk of coronary heart disease. [1-3] In addition, increasing evidence suggests that coffee consumption may protect against type 2 diabetes. [4-8] However, data on the relation between coffee consumption and stroke are sparse. No association has been found between coffee and risk of total stroke among middle-aged healthy men [9] and among patients with type 2 diabetes. [10] By contrast, another study found that consumption of coffee was associated with an increased risk of ischemic stroke among hypertensive men. [11] Finally, in a recent study of male smokers, an association between high coffee consumption and a lower risk of stroke was observed. [12] To our knowledge, the association between coffee and stroke among women has not been examined previously. [13]

In this study, we assessed the association between long-term coffee consumption and risk of stroke over 24 years of follow-up in U.S. women. In order to determine whether caffeine or other components in coffee were responsible for the observed associations, decaffeinated coffee and other caffeinated beverages were also examined. Moreover, given that several studies have associated coffee consumption with increased risk of hypertension, [14] hypercholesterolemia, [15, 16] but reduced risk of type 2 diabetes mellitus, [17] we have examined whether the association between coffee consumption and stroke was modified by these vascular risk factors.

Methods

Study Population

We used data from the Nurses' Health Study (NHS), whose full details have been published elsewhere. [18] Briefly, this cohort was established in 1976 and information from the participants has been updated every 2 years. We used 1980 as the baseline because this was the first year in which information on diet was collected. For the current analysis, we excluded participants with a history of stroke, coronary heart disease, diabetes or cancer at baseline and those with no information about coffee consumption at baseline (N=879), leaving 83,076 women. The Harvard School of Public Health and Brigham and Women's Hospital Human Subjects Committee Review Boards approved the study protocol.

Assessment of coffee consumption

Food frequency questionnaires were sent to the NHS participants in 1980, 1984, 1986, 1990, 1994, 1998, and 2002. In each questionnaire, participants were asked how often on average during the previous year they had consumed coffee and tea. Decaffeinated coffee and different types of caffeinated soft drinks were first assessed in 1984. Using the U.S. Department of Agriculture food composition data, supplemented with other sources, we estimated that the caffeine content was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per can or a 12-ounce bottle of soft drink, and 7 mg per 1-ounce serving of chocolate candy. We assessed the total intake of caffeine by summing the caffeine content for a unit of each food during the previous year multiplied by a weight proportional to the frequency of its consumption. In our validation study, we obtained high correlations between consumption of coffee and other caffeinated beverages estimated from the food frequency questionnaire and consumption estimated from repeated 1-week diet records (coffee, r=0.78; tea, r=0.93; and caffeinated soft drinks, r=0.85). [19] For the present analysis, coffee consumption was categorized into 5 groups: less than 1 cup per month, 1 cup per month to 4 cups per week, 5 to 7 cups per week, 2 to 3

cups per day, and 4 or more cups per day. Food frequency questionnaires were also used to assess the consumption of other foods. Nutrient values were derived from the foods reported and were energy-adjusted using the residual method. [20]

Ascertainment of stroke

Incident stroke was defined as the first nonfatal stroke or stroke death occurring after the baseline questionnaire in 1980 but before June 1, 2004. Women who reported a stroke were asked for permission to access medical records, which were reviewed by a physician without knowledge of the participant's exposure status. Stroke was classified according to criteria of the National Survey of Stroke, [21] which requires evidence of a neurologic deficit with sudden or rapid onset that persisted for more than 24 hours or until death. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded, as were 'silent' strokes discovered only by radiological imaging. Strokes were classified as follows: ischemic stroke (thrombotic or embolic strokes), hemorrhagic stroke (subarachnoid or intraparenchymal hemorrhage), or stroke of undetermined subtype. For each type of stroke, the diagnosis was classified as definite when a CT scan, MRI, angiography, surgery, or autopsy had confirmed the lesion; otherwise, stroke was classified as probable. CT or MRI reports were available for 89% of those with medical records. Cases in which medical record release was refused or for which medical records were unavailable, were classified as probable stroke of undetermined type. In these analyses, 1,909 cases of a first nonfatal stroke were identified: 1,364 (71.4%) were confirmed by medical record review and 545 (28.6%) were classified as probable, corroborated by letter or by telephone.

Deaths were identified through information provided by the next of kin or postal authorities or by systematic searches of the National Death Index. Classification of fatal stroke was confirmed by review of hospital records, autopsy, or death certificate. If information was limited to death certificates or information provided by next of kin with no medical records available, cases were classified as probable. In this analysis, of 371 fatal strokes, 310 (83.5%) were confirmed by medical records and 61 (16.5%) were classified as probable, corroborated by telephone information provided by next of kin or by death certificates.

Of 2,280 total strokes, 1,674 (73.4%) were confirmed on the basis of medical records and 606 (26.6%) were classified as probable on the basis of supporting information. Similar results were obtained when confirmed strokes were examined separately; therefore, confirmed and probable cases were combined for total stroke analyses.

Assessment of medical history, anthropometric data and lifestyle factors

In the baseline questionnaire, we requested information about age, weight and smoking, menopausal status and use of postmenopausal hormone therapy (HT), aspirin use, and personal history of stroke, coronary heart disease, cancer, type 2 diabetes mellitus, hypertension, and hypercholesterolemia. This information has been updated in the biennial follow-up questionnaires. Height was ascertained on the 1976 enrollment questionnaire. Information about treatments for hypertension and hypercholesterolemia was collected in 1988, 1994, 1996, 1998, and 2002. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Physical activity was assessed biennially and reported in hours per week of moderate (e.g., brisk walking) and vigorous exercise (e.g., strenuous sports and jogging). Alcohol intake was assessed every four years and was measured in grams per day. Standard drinks of alcoholic beverages were specified as a can/bottle or glass for beer, 4-oz glass for wine, and one drink or shot for liquor. Detailed information on the validity and reproducibility of the self-reported weight, physical activity, and alcohol consumption has been reported elsewhere. [22-24] In addition, self-reported diagnosis of hypertension, hypercholesterolemia, and type 2 diabetes were found to be reliable in the NHS cohort. [25]26

Statistical analysis—We classified participants according to levels of coffee consumption. We calculated person-years of exposure from the date of return of the baseline questionnaire to the date of death, or June 1, 2004, whichever came first. To reduce within-subject variation and best represent long-term diet, we used the cumulative average of coffee consumption from all available dietary questionnaires up to the start of each 2-year follow-up interval; [27] for example, the average of the 1980 and 1984 intakes was used for the follow-up between 1984 and 1986; the average of the 1980, 1984, and 1986 intakes was used for the follow-up between 1986 and 1990; and so on. When a FFQ had a missing value for coffee, we used the value from the previous questionnaire.

We used Cox proportional hazards models to investigate the association between coffee consumption and incidence of total, hemorrhagic, and ischemic stroke. To control as finely as possible for confounding by age and calendar time, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. We used hazard ratios to estimate relative risks in each category of coffee consumption in comparison with participants in the lowest category of coffee consumption. Multivariable models were adjusted for smoking, body mass index, physical activity, alcohol intake, menopausal status and use of postmenopausal hormone therapy, aspirin use, and dietary factors that have been associated with risk of hypertension and stroke (total energy intake, calcium, potassium, sodium, folate, glycemic load, cereal fiber, whole grain intake, fruits, vegetables, and fish consumption). [28] An additional analysis was performed to further adjust the association between coffee and stroke for potential biological mediators including hypertension, hypercholesterolemia, and type 2 diabetes mellitus. To test for linear trends across categories, we modeled coffee consumption as a continuous variable using the median value of each category of coffee consumption.

We conducted stratified analyses by categories of hypertension, hypercholesterolemia, type 2 diabetes mellitus, smoking, alcohol consumption, and body mass index. We examined interaction between coffee and the categories of the stratification variables with stroke by using likelihood-ratio tests, which compared the nested models with and without cross-product interaction terms. Finally, we also studied the association of caffeine, tea, caffeinated soft drinks, and decaffeinated coffee consumption with stroke. All analyses were performed with the SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. [29] The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

During 24 years of follow-up, we documented 2,280 stroke events, including 426 hemorrhagic, 1224 ischemic, and 630 undetermined type stroke events. In Table 1 we present the characteristics of the NHS participants by levels of coffee consumption in 1990, roughly the midpoint of the follow-up period. Frequent caffeinated coffee consumption was strongly associated with smoking. In addition, women who consumed more coffee were more likely to drink alcohol. Women in the upper categories of caffeinated coffee consumption followed a diet higher in potassium with a lower glycemic load, factors that may reduce risk of stroke. In contrast, women with higher coffee consumption also showed lower intakes of folate and whole grains, which may increase risk of stroke. Caffeinated coffee was consumed by 84% of the subjects in the cohort, whereas 50% of study participants were consumers of decaffeinated coffee, 78% of tea, and 54% of caffeinated soft drinks.

In age-adjusted analyses, higher caffeinated coffee consumption was not associated with risk of total stroke (Table 2). However, after adjustment for smoking as well as other confounders, we found that women who consumed 2 to 3 cups of coffee per day had a 19% lower risk of stroke than women in the lowest category of consumption, while women consuming 4 or more cups of coffee per day had a 20% lower risk of stroke (p for trend= 0.003). After adjustment for hypertension, hypercholesterolemia, and type 2 diabetes, the results were similar although the RR for consumption of 4 or more cups per day became non significant. Moreover, when we analyzed types of strokes, a suggestion of an inverse association was observed for caffeinated coffee consumption and risk of ischemic stroke (p for trend=0.06) with similar attenuation after controlling for the potential biological mediators.

One prior report had suggested a detrimental effect of caffeinated coffee consumption on stroke among hypertensive men;[11] by contrast, in our cohort, we found an inverse association among non-hypertensive women and no association among hypertensive participants. However, the formal test for interaction was nonsignificant (p= 0.29) (Table 3). Similarly, trends were nonsignificant for diabetic and hypercholesterolemic women, although formal interactions terms were negative. Moreover, the inverse association between caffeinated coffee consumption and stroke was observed only among non-smokers and past smokers, but not current smokers (p for interaction= 0.05). Being obese or drinking alcohol did not significantly modify the association between coffee consumption and stroke.

We next studied the relation between total caffeine intake and risk of stroke, and again observed an inverse association (Table 4). However, we cannot attribute this effect solely to caffeine because caffeinated coffee consumption and total caffeine intake are highly correlated (r=0.92). Thus, to elucidate whether caffeine was responsible for the reduced risk of stroke among women consuming caffeinated coffee, we separately assessed the effect of other beverages containing caffeine such as tea and caffeinated soft drinks on stroke; no association was found (Table 4). Finally, we assessed associations for decaffeinated coffee, which has a similar composition to caffeinated coffee except for caffeine. We observed a lower risk of stroke in women who drank moderate amounts of decaffeinated coffee after controlling the analyses for caffeinated coffee consumption.

Because it is possible that some of the effects of caffeinated coffee may be short-term, secondary analyses were performed to assess the association between the most recently reported coffee consumption and stroke; the results were similar to those reported above using cumulative caffeinated coffee consumption. We also stopped updating information on coffee consumption when hypertension, hypercholesterolemia, cancer, diabetes, or heart diseases were diagnosed during the follow-up, with similar results. In addition, no appreciable change in the association was observed after adjustment for medication to treat hypertension (diuretics, beta blockers, calcium channel blockers, ACE inhibitors, and others) and hypercholesterolemia (statins and others). Finally, analyses using only confirmed strokes as the endpoint gave results comparable to the analyses using both confirmed and probable cases of stroke.

Discussion

In this large cohort of women, those who drank moderate to high amounts of coffee had a lower risk of stroke than those who did not consume coffee. This association was only partially mediated by potential biological mediators including high blood pressure, hypercholesterolemia, and type 2 diabetes mellitus. Higher consumption of decaffeinated coffee, but not tea or caffeinated soft drinks was also associated with a generally lower stroke risk, supporting the hypothesis that components in coffee other than caffeine may lower risk of stroke.

Few studies have addressed the association between coffee consumption and risk of stroke (Table 5). Those analyses have been performed in groups with very different risk of stroke, such as healthy people, patients with type 2 diabetes, hypertensive individuals, and even smokers. In our analyses, we were able to assess long-term coffee consumption in a large population of women and evaluate possible differences in association between healthy participants and those with the above vascular risk factors.

Hypertension is a major risk factor for stroke. [13] However, the relationship between long-term coffee consumption and hypertension remains uncertain because few cohort studies have analyzed this association. Klag et al., [14] using the Johns Hopkins Precursors Study, found that consumption of coffee was cross-sectionally associated with a slightly higher blood pressure, although the association with incident hypertension was unclear. Winkelmayer et al., [30] using data from the Nurses' Health Study and Nurses' Health Study II, found that coffee consumption was not associated with an increased risk of hypertension in women [RR (95% CI) for consumption of ≥6 cups/d: 0.88 (0.80-0.98) vs. <1 cup/d in NHS, and 0.91 (0.80-1.04) in NHS II]. Hu et al. [31] examined the association between coffee and the incidence of antihypertensive drug use. The authors concluded that consumptions higher than 2 cups of coffee per day increased the risk of antihypertensive drug treatment [RRs (95% CI) for consumption of 2-3, 4-5, 6-7, and ≥8 cups of coffee/day were 1.29 (1.09-1.54), 1.26 (1.06-1.49), 1.24 (1.04-1.48) and 1.14 (0.94-1.37) as compared with 0-1 cups/day)]. Finally, Uiterwaal et al., [32] found that women abstainers and heavy consumers (>6 cups of coffee per day) had lower risk of hypertension than moderate consumers (1 to 3 cups/d). Most of these studies suggest that although caffeine intake acutely increases blood pressure, [33] regular exposure to caffeine can attenuate this effect. In addition, a study found that consumption of 3 cups of coffee per day increased the risk of stroke among hypertensive patients [11] (RR=2.1, 95% CI: 1.2-3.7). This study pointed to caffeine as potentially responsible for this association by increasing cardiovascular resistance and decreasing cerebral blood flow, which impair the already damaged vascular system in these patients. [34] In our study, an inverse association between coffee consumption and risk of stroke was only apparent in women without hypertension, but no increase in risk of stroke was seen among hypertensive participants. More research is necessary to elucidate whether coffee may have a detrimental effect on these patients.

We also examined the effect of coffee on stroke separately in women with and without diabetes mellitus. Long-term studies have consistently found an association between higher coffee consumption and lower risk for type 2 diabetes. [17] One study has assessed the effect of coffee on fatal stroke among diabetic patients, finding no association even with consumptions as high as 7 cups/day. [10] Similarly, in our study, we did not find association between coffee and stroke in the subsample of diabetic patients. Although coffee has been shown to have a beneficial effect on glucose metabolism, [17] the null association between coffee and stroke found in these patients may reflect the important effect of diabetes on atherosclerosis and hypercoagulability, among other vascular alterations, [35] which neutralizes any beneficial effect of coffee in this population.

Hypercholesterolemia is another important risk factor for stroke. Although short-term clinical trials have confirmed the cholesterol-raising effect of diterpenes present in boiled coffee, [15] no long-term studies have assessed this association. In a previous cross-sectional study, [1] we did not find increased levels of total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol among individuals consuming non-paper filtered coffee compared to non consumers. In the present study, we found an inverse association between coffee and stroke among participants without hypercholesterolemia but not among those with the risk factor. We can only speculate that the effect of coffee might be of a lower relevance for patients with a higher degree of atheromatosis.

Lastly, smoking is a strong confounder in the study association because it is a potent risk factor for stroke and because smoking is more frequent among coffee drinkers. Therefore, stratified analyses were performed to more thoroughly eliminate residual confounding. Coffee consumption was associated with a substantially lower risk of stroke among non-smokers, but not among current smokers. We hypothesize that the potential benefit of coffee reducing the risk of stroke cannot counterbalance the detrimental effect of smoking on health.

Several mechanisms might help to explain the reduced incidence of stroke that we observed among individuals who consumed coffee. Some substances in coffee may have beneficial effects on glucose metabolism, inflammation and endothelial dysfunction. For example, habitual coffee consumption has been associated with higher insulin sensitivity. [36] In addition, we previously reported an inverse association of caffeinated coffee consumption with surface leukocyte adhesion molecules (E-selectin) and with C-reactive protein (CRP), an inflammatory marker in diabetic women, as well as an inverse association of decaffeinated coffee consumption with CRP in healthy women. [37] Furthermore, the phenolic compounds of coffee (chlorogenic acid, ferulic acid, and p-coumaric acid) have strong antioxidant capacity. [38] The modest inverse association between decaffeinated coffee consumption and risk of stroke in our study supports the hypothesis that components in coffee other than caffeine may be responsible for the potential beneficial effect of coffee on stroke risk.

The present study had several strengths for the examination of the association between coffee consumption and risk of stroke. First, the study included multiple repeated measures of coffee consumption limiting misclassification of coffee consumption. Some measurement error in the assessment of coffee consumption may still have occurred because data on consumption was self-reported. However, results from our validation study indicate that coffee was among the most accurately reported foods in the dietary questionnaire. [19] Second, we were able to control for potential confounders in more detail than in earlier studies, because information on risk factors has been updated every 2 years; however, residual confounding by other factors associated with coffee consumption cannot be excluded. Third, data collection on incident strokes was thorough and a high percentage of events were confirmed by imaging studies. The possibility that reverse causation may have biased our results should be considered. For example, women who were diagnosed with hypertension may have lowered their consumption of caffeinated coffee as a result of the diagnosis. We addressed this issue by examining the association between coffee and risk of stroke among non-hypertensive women only, as well as performing additional analyses that stopped updating consumption when hypertension was diagnosed. The associations between coffee and risk of stroke were similar to those in the main analysis.

In conclusion, in this long-term follow-up study, coffee consumption was not associated with an increased risk of stroke. In contrast, we observed that women who regularly consumed coffee had a modestly lower risk of stroke than non-consumers. Our data support the hypothesis that components in coffee other than caffeine may lower risk of stroke, although the association was modest and the biological mechanism is unclear. These results should be supported by further research before considering the possible implications for public health and clinical practice.

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Table 1

Midpoint characteristics (in 1990) by levels of caffeinated coffee consumption among participants in the NHS.

	Caffeinated coffee consumption, cups.				
	<1/mo	**1/mo-4/wk**	**5-7/wk**	**2-3/d**	**≥4/d**
Mean age, y	55	56	56	56	56
BMI, kg/m^2	25.7	25.6	25.6	25.1	24.7
Physical activity*, h/w	2.8	2.8	2.7	2.7	2.6
Alcohol intake, g/d	2.8	4.0	5.3	6.6	5.8
Current smoker, %	8	9	12	22	39
Hypertension, %	17	19	18	14	10
Hypercholesterolemia, %	26	30	30	26	21
Diabetes, %	2	2	2	2	1
Aspirin use†, %	46	53	55	53	44
Postmenopausal hormone use, %	25	28	28	25	21
Antihypertensive medication, %					
Diuretics	11	14	13	10	6
Beta blockers	8	9	8	6	3
Calcium channel blockers	2	3	2	2	1
ACE inhibitors	2	2	2	2	1
Other	2	2	2	1	1
Antihypercholesterolemic medication, %	2	2	2	1	1
Caffeinated coffee, cup/d	0	0.32	1.48	2.95	4.88
Decaffeinated coffee, cup/d	0	0.79	0.53	0.05	0
Tea, cup/d	0.66	0.50	0.38	0.25	0.09
Cola beverages, can/d	0.07	0.07	0.10	0.14	0.12
Caffeine, mg/d	102	134	274	469	747
Calcium, mg/d	895	922	901	874	837
Potassium, mg/d	2651	2754	2850	2969	3161
Sodium, mg/d	1816	1856	1878	1864	1793
Folate, µg/d	404	420	397	372	345
Glycemic load	102	99	96	92	89
Cereal fiber, g/d	3.9	4.1	3.9	3.6	3.3

	Caffeinated coffee consumption, cups.				
	<1/mo	**1/mo-4/wk**	**5-7/wk**	**2-3/d**	**≥4/d**
Whole grains, g/d	17.1	17.4	16.0	14.4	13.0
Fruits, serving/d	0.88	0.94	0.90	0.84	0.75
Vegetables, serving/d	1.73	1.78	1.76	1.71	1.67
Fish, serving/d	0.19	0.23	0.21	0.19	0.16

Values are means unless otherwise indicated. Data, except age, were directly standardized to the age distributions of the entire cohort.

* Physical activity includes moderate and vigorous intensity activity.

† Aspirin use 1 or more times per week.

Table 2

Relative risks (95% confidence interval) of types of stroke according to caffeinated coffee consumption in the NHS, 1980-2004.

	Caffeinated coffee consumption, cups.					
	<1/mo	**1/mo-4/wk**	**5-7/wk**	**2-3/d**	**≥4/d**	**P value for Trend**
Total stroke						
Person-yr	303,293	236,388	586,501	541,298	222,706	
Cases, n	329	335	802	593	221	
Age adjusted	1.0	0.98 (0.84-1.14)	0.92 (0.81-1.04)	0.93 (0.81-1.06)	1.11 (0.94-1.32)	0.36
Age and smoking adjusted	1.0	0.97 (0.83-1.13)	0.87 (0.77-1.00)	0.80 (0.70-0.92)	0.82 (0.69-0.98)	0.003
Multivariable model 1*	1.0	0.98 (0.84-1.15)	0.88 (0.77-1.02)	0.81 (0.70-0.95)	0.80 (0.64-0.98)	0.003
Multivariable model 2†	1.0	0.96 (0.82-1.13)	0.88 (0.77-1.02)	0.84 (0.72-0.98)	0.85 (0.69-1.06)	0.05
Hemorrhagic						
Cases, n	57	51	141	124	53	
Age adjusted	1.0	0.98 (0.67-1.43)	1.06 (0.78-1.45)	1.14 (0.83-1.56)	1.37 (0.94-1.99)	0.05
Age and smoking adjusted	1.0	0.96 (0.66-1.41)	1.00 (0.73-1.37)	0.96 (0.70-1.32)	0.95 (0.65-1.41)	0.78
Multivariable model 1*	1.0	1.02 (0.68-1.52)	1.03 (0.73-1.46)	1.01 (0.70-1.47)	0.79 (0.47-1.33)	0.43
Multivariable model 2†	1.0	1.01 (0.68-1.51)	1.03 (0.73-1.45)	1.02 (0.70-1.48)	0.81 (0.48-1.36)	0.49
Ischemic						
Cases, n	171	182	449	308	114	
Age adjusted	1.0	0.99 (0.81-1.23)	0.95 (0.80-1.14)	0.91 (0.76-1.10)	1.14 (0.90-1.45)	0.65
Age and smoking adjusted	1.0	0.98 (0.80-1.21)	0.91 (0.76-1.09)	0.80 (0.66-0.97)	0.85 (0.67-1.09)	0.03
Multivariable model 1*	1.0	0.97 (0.78-1.20)	0.90 (0.75-1.09)	0.79 (0.64-0.97)	0.86 (0.64-1.14)	0.06
Multivariable model 2†	1.0	0.95 (0.77-1.17)	0.90 (0.75-1.09)	0.82 (0.67-1.01)	0.94 (0.71-1.26)	0.32

*Adjusted for: age (5-year categories), smoking status (never, past, and current 1-14, 15-24, and ≥25 cigarettes/day), body mass index (<23.0, 23.0-24.9, 25.0-27.9, 28.0-29.9, ≥30.0 kg/m^2), physical activity (<1.0, 1.0-1.9, 2.0-3.9, 4.0-6.9, ≥7.0 hours/week), alcohol intake (never, 0.1-4.9, 5.0-9.9, 10.0-14.9, 15.0-29.9, ≥30.0 g/d), menopausal status and use of hormone replacement therapy (premenopausal women, post without HT, post with past HT, post with current HT), aspirin use, total caloric intake, and quintiles of calcium, potassium, sodium, and folate intake, glycemic load, whole grain intake, and tertiles of fruits, vegetables, and fish consumption.

†Additional adjustment for potential intermediates: high blood pressure, hypercholesterolemia, and type 2 diabetes mellitus.

Table 3

Relative risks (95% confidence interval) of total stroke according to caffeinated coffee consumption, stratified by hypertension, diabetes, hypercholesterolemia, smoking status, BMI, and alcohol consumption in the NHS 1980-2004.

	Caffeinated coffee consumption, cups						
	<1/mo	**1/mo-4/wk**	**5-7/wk**	**2-3/d**	**≥4d**	**P value for Trend**	**P for interaction**
Hypertension status							
Nonhypertensive (n events=1380)	1.0	0.99 (0.80-1.22)	0.87 (0.72-1.04)	0.75 (0.61-0.91)	0.72 (0.55-0.94)	0.001	0.29
Hypertensive (n events=900)	1.0	0.97 (0.76-1.24)	0.90 (0.72-1.11)	0.98 (0.77-1.24)	1.10 (0.76-1.58)	0.53	
Diabetes status							
Nondiabetic (n events=2083)	1.0	1.03 (0.87-1.23)	0.93 (0.79-1.09)	0.86 (0.72-1.02)	0.79 (0.62-1.01)	0.009	0.77
Diabetic (n events=197)	1.0	0.78 (0.48-1.29)	0.82 (0.53-1.26)	0.86 (0.51-1.45)	1.16 (0.47-2.81)	0.74	
Hypercholesterolemia status							
Nonhypercholesterolemic (n events=1598)	1.0	1.01 (0.83-1.22)	0.88 (0.74-1.04)	0.78 (0.65-0.94)	0.77 (0.60-0.98)	0.003	0.79
Hypercholesterolemic (n events=682)	1.0	0.97 (0.73-1.28)	0.92 (0.71-1.18)	0.91 (0.69-1.21)	0.89 (0.58-1.35)	0.55	
Smoking status							
Never and past (n events=1148)	1.0	0.93 (0.76-1.14)	0.83 (0.69-0.99)	0.84 (0.68-1.03)	0.57 (0.39-0.84)	0.001	0.05
Current* (n events=503)	1.0	0.86 (0.52-1.40)	1.03 (0.70-1.50)	0.89 (0.61-1.31)	0.97 (0.63-1.48)	0.85	
BMI							
<30 kg/m^2 (n events=1849)	1.0	0.97 (0.80-1.17)	0.93 (0.78-1.09)	0.82 (0.68-0.98)	0.81 (0.62-1.05)	0.02	0.35
≥30 kg/m^2 (n events=431)	1.0	1.14 (0.80-1.62)	0.85 (0.61-1.17)	0.91 (0.63-1.29)	0.62 (0.35-1.10)	0.08	
Alcohol							
Abstainer (n events=573)	1.0	0.92 (0.70-1.21)	0.76 (0.60-0.97)	0.69 (0.52-0.92)	0.60 (0.40-0.91)	0.005	0.72
Drinker (n events=1707)	1.0	1.04 (0.85-1.27)	0.95 (0.79-1.13)	0.88 (0.72-1.06)	0.88 (0.68-1.14)	0.07	

Models adjusted for the same covariates as in model 1 (Table 2), except for the stratification variable.

*Additional adjustment for no. of cigarettes/d. The number of events is different because of missing values for smoking status.

Table 4

Relative risks (95% confidence interval) of total stroke according to caffeine intake, tea, cola beverages, and decaffeinated coffee consumption in the NHS 1980-2004.

	Beverage consumption, cups.					
	<1/mo	**1/mo-4/wk**	**5-7/wk**	**2-3/d**	**≥4/d**	**P value for trend**
Caffeine intake (quintiles)						
Median caffeine intake (mg/d)	71	191	318	423	687	
Person-yr	377,854	377,540	377,194	378,933	378,664	
Cases, n	493	483	482	432	390	
Age-adjusted	1.0	0.93 (0.82-1.06)	0.94 (0.83-1.07)	0.94 (0.82-1.07)	0.98 (0.86-1.12)	0.96
Multivariable*	1.0	0.90 (0.79-1.02)	0.87 (0.76-1.00)	0.84 (0.72-0.96)	0.73 (0.62-0.85)	<0.001
Tea						
Person-yr	418,413	799,820	479,281	155,061	37,611	
Cases, n	503	1035	586	127	29	
Age-adjusted	1.0	0.92 (0.83-1.03)	0.91 (0.81-1.03)	0.84 (0.69-1.02)	0.98 (0.67-1.42)	0.10
Multivariable†	1.0	1.07 (0.95-1.20)	1.05 (0.92-1.20)	0.92 (0.74-1.14)	0.79 (0.49-1.29)	0.19
Caffeinated soft drinks‡						
Person-yr	757,580	597,423	148,236	33,372		
Cases, n	1111	770	161	30	-	
Age-adjusted	1.0	0.97 (0.88-1.07)	1.06 (0.90-1.26)	1.26 (0.88-1.82)		0.15
Multivariable†	1.0	1.04 (0.94-1.16)	1.04 (0.87-1.24)	1.08 (0.74-1.57)		0.66
Decaffeinated coffee‡						
Person-yr	740,681	377,235	306,534	112,161		
Cases, n	1023	517	404	128	-	
Age-adjusted	1.0	0.86 (0.77-0.96)	0.77 (0.69-0.87)	0.84 (0.70-1.01)		0.002
Multivariable†	1.0	0.98 (0.87-1.10)	0.86 (0.76-0.98)	0.89 (0.73-1.08)		0.05

*Model adjusted for the same covariates as in model 1 (Table 2).

†Models adjusted for the same covariates as in model 1 (Table 2), plus caffeinated coffee consumption.

‡Follow-up from 1984.

Table 5

Cohort studies addressing the association between caffeinated coffee consumption and risk of stroke.[a]

Author, country	Sex, age (years)	N	Exposure	Outcome	No. of cases	Mean follow-up (years)	Adjustment for confounding	Multivariate-adjusted result	Comments
Grobbee et al. (9), US	Healthy men, 40-75	45,589	Caffeinated coffee at baseline	Fatal and nonfatal stroke	54	2	Age, SMK, BMI, history of diabetes mellitus, alcohol consumption, parental history of MI, specific health profession, and dietary intake of energy, cholesterol, and saturated, monounsaturated, and polyunsaturated fat.	For consumption of ≥4 cups/d, the RR of fatal and nonfatal stroke was 0.28 (0.06-1.26), compared to non consumption.	No association between coffee and fatal and nonfatal stroke.
Bidel et al. (10), Finland	Diabetic men, 25-74	3,837	Total coffee at baseline	Fatal stroke	210	20.8	Age, sex, BMI, SBP, serum total cholesterol, education, SMK, and alcohol and tea consumption.	For consumption of ≥7 cups/d, the RR of fatal stroke was 0.90 (0.56-1.45), compared to 0-2 cups/d.	No association between coffee and fatal stroke.
Hakim et al. (11), US	Hypertensive and nonsmoker men, 55-68	499	Total coffee at baseline	Ischemic stroke Hemorrhagic stroke	76 -	25	Age, SBP, serum total cholesterol, triglycerides, diabetes, alcohol use, and physical activity.	For consumption of 24 oz./d, the RR of ischemic stroke was 2.1 (1.2-3.7), compared to non consumption. RR for hemorrhagic stroke not provided.	Positive association between coffee and ischemic stroke. No association between coffee and hemorrhagic stroke.
Larsson et al. (12), Finland	Male smokers, 50-69	26,556	Total coffee at baseline	Ischemic stroke Intracerebral hemorrhages Subarachnoid hemorrhages	2702 383 196	13.6	Age, vitamin supplementation use, SMK, BMI, SBP, DBP, serum total cholesterol, HDL, history of diabetes and CHD, physical activity, and alcohol and tea consumption.	For consumption of ≥8 cups/d, the RR of ischemic stroke was 0.77 (0.66-0.90), the RR of intracerebral hemorrhages was 0.98 (0.66-1.47), and the RR of subarachnoid hemorrhages was 1.18 (0.63-2.20), compared to <2 cups/d.	Inverse association between coffee and ischemic stroke. No association between coffee and intracerebral or subarachnoid hemorrhage.

[a] Obtained from a MEDLINE search through June 2008 using the key words *coffee* and *caffeine* in combination with *stroke*.

SMK: smoking; BMI: body mass index; MI: myocardial infarction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high density lipoprotein; CHD: coronary heart disease.