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Stroke 2011, 42:908-912: originally published online March 10, 2011

doi: 10.1161/STROKEAHA.110.603787

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ISSN: 1524-4628

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Coffee Consumption and Risk of Stroke in Women

Susanna C. Larsson, PhD; Jarmo Virtamo, MD; Alicja Wolk, DMSc

Background and Purpose—Coffee consumption has been inconsistently associated with stroke incidence and mortality in previous studies. We investigated the association between coffee consumption and stroke incidence in the Swedish Mammography Cohort.

Methods—We prospectively followed 34 670 women without a history of cardiovascular disease or cancer at baseline in 1997. Coffee consumption was assessed in 1997 using a self-administered questionnaire. Incident stroke cases were ascertained from the Swedish Hospital Discharge Registry.

Results—During a mean follow-up of 10.4 years, we ascertained 1680 stroke events, including 1310 cerebral infarctions, 154 intracerebral hemorrhages, 79 subarachnoid hemorrhages, and 137 unspecified strokes. After adjustment for other risk factors, coffee consumption was associated with a statistically significant lower risk of total stroke, cerebral infarction, and subarachnoid hemorrhage but not intracerebral hemorrhage. The multivariable relative risks of total stroke across categories of coffee consumption (<1 cup/day, 1 to 2 cups/day, 3 to 4 cups/day, and ≥ 5 cups/day) were 1.00, 0.78 (95% CI, 0.66 to 0.91), 0.75 (95% CI, 0.64 to 0.88), and 0.77 (95% CI, 0.63 to 0.92, respectively; P for trend=0.02). The association between coffee consumption and cerebral infarction was not modified by smoking status, body mass index, history of diabetes or hypertension, or alcohol consumption.

Conclusions—These findings suggest that low or no coffee consumption is associated with an increased risk of stroke in women. (*Stroke*. 2011;42:908-912.)

Key Words: coffee ■ epidemiology ■ prospective studies ■ stroke ■ women

Accumulating evidence indicates that coffee consumption may decrease the risk of Type 2 diabetes¹ but probably has no association with coronary heart disease.² Habitual coffee consumption could potentially reduce the risk of stroke by increasing insulin sensitivity³ and reducing inflammation.^{4,5} Furthermore, the phenolic compounds of coffee have antioxidant properties and may improve endothelial function.⁶ However, whether coffee consumption affects the risk of stroke is unclear. Epidemiological studies of coffee consumption in relation to stroke incidence⁷⁻⁹ or mortality¹⁰⁻¹⁴ have yielded inconsistent results. This may be because of different outcomes (incidence versus mortality) and different study populations (healthy versus diabetics or hypertensive). To our knowledge, only 1 previous prospective study has assessed the association between coffee consumption and the incidence of stroke among healthy women.⁷ Given that coffee is 1 of the most popular beverages consumed worldwide, even small health effects of substances in coffee may have large public health consequences.

The aim of this study was to examine the association between coffee consumption and incidence of stroke in a population-based prospective cohort study of Swedish women. We investigated whether the association was modi-

fied by smoking, body mass index, history of diabetes or hypertension, or alcohol consumption.

Subjects and Methods

Study Population

We used data from the Swedish Mammography Cohort. Details of this population-based prospective cohort study have been reported elsewhere.¹⁵ Briefly, the cohort was established between 1987 and 1990, when all women born between 1914 and 1948 and residing in central Sweden (Västmanland and Uppsala counties) received a mailed questionnaire on diet. In late Fall of 1997, the 56 030 participants who were still alive and living in the study area received a new expanded questionnaire that included approximately 350 items concerning diet and other lifestyle factors; 39 227 women (70%) completed the second questionnaire. Among women who were still alive in 1997, those who completed the 1997 questionnaire were on average younger, were slightly more likely to have a university education, and had a lower body mass index at baseline than those who did not complete the questionnaire. The mean coffee consumption at baseline was identical (mean, 2.4 cups/day) among women who completed the 1997 questionnaire and among those who did not.

For the present analysis, we used 1997 as the baseline because information on cigarette smoking and some other risk factors for stroke was not obtained at baseline. We excluded women with an erroneous or a missing national identification number; those with a history of stroke, coronary heart disease, or cancer at baseline in 1997; and those with implausible values for total energy intake (ie,

Received September 25, 2010; final revision received November 8, 2010; accepted November 15, 2010.

From the Division of Nutritional Epidemiology (S.C.L., A.W.), National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; and the Department of Chronic Disease Prevention (J.V.), National Institute for Health and Welfare, Helsinki, Finland.

Correspondence to Susanna C. Larsson, PhD, Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-17177 Stockholm, Sweden. E-mail susanna.larsson@ki.se

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.110.603787

3 SDs from the log_e-transformed mean energy intake). This left 34 670 women aged 49 to 83 years for the analysis. The study was approved by the Ethical Review Board at the Karolinska Institutet (Stockholm, Sweden).

Baseline Data Collection

The 1997 questionnaire included questions on education, weight, height, cigarette smoking, physical activity, aspirin use, history of diabetes and hypertension, family history of myocardial infarction before 60 years of age, alcohol consumption, and diet. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters. Pack-years of smoking history were calculated as the number of packs of cigarettes smoked per day multiplied by the number of years of smoking. The participants reported their level of activity at work, home/housework, walking/bicycling, and exercise in the year before study enrollment. The questionnaire also included questions on inactivity (watching TV/reading) and hours per day of sleeping and sitting/lying down. The reported time per day reported by the subject to have engaged in each activity was multiplied by the activity's typical energy expenditure requirement expressed in metabolic equivalents. The metabolic equivalent-hours for all of the individual activities reported by the subject were then added together to create a metabolic equivalent-hours per day (24-hour) score.¹⁶

Assessment of Coffee Consumption

Coffee consumption was assessed using a self-administered food-frequency questionnaire that included 96 foods and beverages. For coffee, participants were asked to indicate how many cups of coffee per day or per week they consumed during the past year. The questionnaire did not inquire about the type of coffee consumed (eg, regular or decaffeinated coffee) because consumption of decaffeinated coffee in the Swedish population is very low. In our validation study, the Pearson correlation coefficient between the food-frequency questionnaire and the mean of 4 1-week diet records was 0.6 for coffee (A. Wolk, unpublished data).

Case Ascertainment and Follow-Up

Incident cases of first stroke that occurred between January 1, 1998, and December 31, 2008, were ascertained by linkage of the study cohort with the Swedish Hospital Discharge Registry, which provides almost complete coverage of the discharges. The International Classification of Diseases, 10th Revision, was used to identify stroke events. The stroke events were classified as cerebral infarction (International Classification of Diseases, 10th Revision, code I63), intracerebral hemorrhage (I61), subarachnoid hemorrhage (I60), and unspecified stroke (I64). Information on dates of death was obtained from the Swedish Cause of Death Registry.

Statistical Analysis

Person-time of follow-up for each participant was calculated from January 1, 1998, to the date of the first stroke event, death, or end of follow-up (December 31, 2008), whichever occurred first. We used Cox proportional hazard models with age as the time scale to estimate the relative risks (RRs) with 95% CIs of stroke by categories of coffee consumption. Entry time was defined as a subject's age in months at start of follow-up, and exit time was defined as a subject's age in months at stroke diagnosis, death, or end of follow-up. The proportional hazards assumption was tested and was found to be satisfied for all variables except diabetes. We adjusted for diabetes by stratification in the Cox model. The multivariable model included the following variables: smoking status and pack-years of smoking (never; past <20, 20 to 39, or ≥40 pack-years; or current <20, 20 to 39, or ≥40 pack-years); education (less than high school, high school, or university); body mass index (<20, 20 to 24.9, 25 to 29.9, or ≥30 kg/m²); total physical activity (metabolic equivalent hours/day, quartiles); self-reported history of hypertension (yes or no); aspirin use (yes or no); family history of myocardial infarction before 60 years of age (yes or no); intakes of total energy (kcal/day, continuous variable) and alcohol (non-

Table 1. Baseline Characteristics* of 34 670 Women in the Swedish Mammography Cohort by Coffee Consumption in 1997

Characteristic	Daily Coffee Consumption, No. of Cups			
	<1	1 to 2	3 to 4	≥5
Coffee, cups/day	0.2	1.8	3.5	6.1
Age, years	61.6	62.2	61.3	59.2
Education, university, %	25.2	21.9	18.0	15.0
Current smoker, %	16.4	17.9	23.9	37.4
Body mass index, kg/m ²	25.0	24.9	25.0	25.2
Total physical activity, MET hours/day	42.3	42.3	42.6	43.1
History of diabetes, %	3.4	3.3	3.0	3.1
Hypertension, %	20.6	21.3	18.9	18.0
Aspirin use, %	49.3	49.5	48.7	51.5
Family history of myocardial infarction, %	17.2	16.3	16.3	17.2
Total energy, kcal/day	1665	1680	1777	1855
Alcohol intake, g/day	3.6	4.6	4.2	3.8
Red meat intake, g/day	65	64	66	68
Fish intake, servings/day	0.3	0.3	0.3	0.3
Fruit intake, servings/day	2.1	2.1	2.0	1.9
Vegetable intake, servings/day	3.4	3.3	3.2	3.1

MET indicates metabolic equivalent of energy expenditure (kcal/kg×h).

*Age-standardized to the age distribution of participants at baseline. All values are means if not otherwise indicated.

drinkers or <3.4, 3.4 to 9.9, or ≥10.0 g/day); and quartiles of red meat, fish, fruits, and vegetables. Tests for trends across categories were conducted by modeling coffee consumption as a continuous variable using the median value of each category of coffee.

We conducted stratified analyses to assess whether the association of coffee consumption with stroke risk was modified by smoking status (never/past or current), body mass index (<30 or ≥30 kg/m²), diabetes (yes or no), hypertension (yes or no), and alcohol consumption (abstainer or drinker). To test the statistical significance of interactions on a multiplicative scale, we used the log likelihood ratio test comparing the models with or without interaction terms. All statistical analyses were performed using SAS Version 9.1 (SAS Institute Inc, Cary, NC). All probability values were 2-sided.

Results

During a mean follow-up of 10.4 years, we ascertained 1680 stroke events, including 1310 cerebral infarctions, 154 intracerebral hemorrhages, 79 subarachnoid hemorrhages, and 137 unspecified strokes. The baseline characteristics of the study cohort by categories of coffee consumption are presented in Table 1. The median daily coffee consumption was 3 cups (interquartile range, 2 to 4 cups). Compared with women with a low coffee consumption, those with a high consumption were less likely to have a university education and more likely to be smokers. They also were somewhat less likely to have a history of diabetes or hypertension and consumed less fruits and vegetables.

The risk of total stroke was statistically significantly associated with smoking (current versus never smoking, multivariable RR, 1.38; 95% CI, 1.22 to 1.57), education (university versus primary school, multivariable RR, 0.74; 95% CI, 0.61 to 0.89), and history of hypertension (multivari-

Table 2. Relative Risks and 95% CIs of Total Stroke and Stroke Subtypes by Coffee Consumption in the Swedish Mammography Cohort, 1998 to 2008

	Daily Coffee Consumption, No. of Cups				<i>P</i> for Trend
	<1	1 to 2	3 to 4	≥5	
Total stroke					
Person-years	33 807	132 857	135 678	56 671	
Cases, no.	205	653	607	215	
Age-adjusted	1.0	0.77 (0.66 to 0.91)	0.77 (0.66 to 0.90)	0.84 (0.69 to 1.01)	0.21
Age- and smoking-adjusted	1.0	0.77 (0.66 to 0.90)	0.76 (0.65 to 0.89)	0.79 (0.65 to 0.96)	0.05
Multivariable model*	1.0	0.78 (0.66 to 0.91)	0.75 (0.64 to 0.88)	0.77 (0.63 to 0.92)	0.02
Cerebral infarction					
Cases, no.	157	505	485	163	
Age-adjusted	1.0	0.78 (0.65 to 0.93)	0.81 (0.68 to 0.97)	0.85 (0.68 to 1.05)	0.38
Age- and smoking-adjusted	1.0	0.78 (0.65 to 0.93)	0.80 (0.67 to 0.96)	0.80 (0.64 to 1.00)	0.15
Multivariable model*	1.0	0.79 (0.66 to 0.94)	0.80 (0.66 to 0.96)	0.79 (0.63 to 0.98)	0.08
Total hemorrhagic stroke†					
Cases, no.	28	98	74	33	
Age-adjusted	1.0	0.86 (0.57 to 1.31)	0.67 (0.44 to 1.04)	0.83 (0.50 to 1.37)	0.34
Age- and smoking-adjusted	1.0	0.85 (0.56 to 1.30)	0.65 (0.42 to 1.00)	0.75 (0.45 to 1.24)	0.17
Multivariable model*	1.0	0.83 (0.54 to 1.26)	0.61 (0.39 to 0.94)	0.67 (0.40 to 1.13)	0.08
Intracerebral hemorrhage					
Cases, no.	16	63	50	25	
Age-adjusted	1.0	0.97 (0.56 to 1.67)	0.81 (0.46 to 1.42)	1.18 (0.63 to 2.22)	0.62
Age- and smoking-adjusted	1.0	0.96 (0.56 to 1.66)	0.80 (0.46 to 1.41)	1.15 (0.61 to 2.17)	0.69
Multivariable model*	1.0	0.95 (0.55 to 1.65)	0.77 (0.44 to 1.36)	1.07 (0.56 to 2.03)	0.86
Subarachnoid hemorrhage					
Cases, no.	12	35	24	8	
Age-adjusted	1.0	0.73 (0.38 to 1.40)	0.49 (0.25 to 0.99)	0.41 (0.17 to 1.00)	0.02
Age- and smoking-adjusted	1.0	0.72 (0.37 to 1.38)	0.45 (0.22 to 0.90)	0.31 (0.13 to 0.77)	0.004
Multivariable model*	1.0	0.68 (0.35 to 1.32)	0.40 (0.20 to 0.81)	0.27 (0.11 to 0.67)	0.002

*Adjusted for age; smoking status and pack-years of smoking; education; body mass index; total physical activity; history of diabetes; history of hypertension; aspirin use; family history of myocardial infarction; and intakes of total energy, alcohol, red meat, fish, fruits, and vegetables.

†Intracerebral hemorrhage and subarachnoid hemorrhage combined.

able RR, 1.58; 95% CI, 1.43 to 1.76). Obesity was associated with an increased risk of cerebral infarction (≥ 30 kg/m² versus 20 to 24.9 kg/m², multivariable RR, 1.28; 95% CI, 1.07 to 1.52), and a family history of coronary heart disease was positively associated with risk of intracerebral hemorrhage (multivariable RR, 1.61; 95% CI, 1.06 to 2.45). Aspirin use and total physical activity were not statistically significantly associated with total stroke or any stroke subtype.

The association between coffee consumption and risk of total stroke and stroke subtypes is shown in Table 2. There was no statistically significant association between consumption of coffee and risk of stroke in the age-adjusted analysis. However, after adjustment for smoking (main confounder) and other risk factors, women who consumed 1 to 2 cups, 3 to 4 cups, or >5 cups of coffee per day had a statistically significant 22% to 25% lower risk of stroke compared with those who drank <1 cup of coffee per day. Coffee consumption was associated with decreased risk of cerebral infarction and subarachnoid hemorrhage but not intracerebral hemorrhage. When we compared women who consumed ≥ 1 cups

of coffee per day with those who consumed <1 cup per day, the multivariable RR of total stroke was 0.76 (95% CI, 0.66 to 0.88). The association between coffee consumption and risk of total stroke did not vary statistically significantly by smoking status, body mass index, history of diabetes or hypertension, or alcohol consumption (Table 3).

Discussion

In this population-based cohort of Swedish women, women who consumed ≥ 1 cups of coffee daily had a lower risk of stroke compared with women who consumed <1 cup of coffee daily. There was no dose-response relationship between coffee consumption and risk of total stroke; rather, the risk appeared to be increased among women with low or no consumption of coffee. An inverse association between coffee consumption and stroke was observed for cerebral infarction and subarachnoid hemorrhage but not intracerebral hemorrhage. The association was not modified by smoking status, body mass index, history of diabetes or hypertension, or alcohol consumption.

Table 3. Relative Risks* and 95% CIs of Cerebral Infarction by Coffee Consumption Stratified by Smoking Status, Body Mass Index, Diabetes, Hypertension, and Alcohol Consumption in the Swedish Mammography Cohort, 1998 to 2008

	Daily Coffee Consumption, No. of Cups				P for Trend	P for Interaction
	<1	1 to 2	3 to 4	≥5		
Smoking status						
Never and past (no. of events† 1010)	1.0	0.80 (0.65 to 0.97)	0.81 (0.66 to 0.99)	0.79 (0.61 to 1.02)	0.13	0.66
Current (no. of events 259)	1.0	1.08 (0.65 to 1.81)	1.10 (0.66 to 1.84)	1.12 (0.65 to 1.94)	0.72	
Body mass index, kg/m²						
<30 (no. of events 1091)	1.0	0.85 (0.70 to 1.05)	0.82 (0.67 to 1.01)	0.83 (0.64 to 1.06)	0.17	0.10
≥30 (no. of events 182)	1.0	0.52 (0.33 to 0.80)	0.71 (0.46 to 1.09)	0.56 (0.32 to 0.97)	0.16	
Diabetes status						
Nondiabetic (no. of events 1218)	1.0	0.79 (0.65 to 0.95)	0.80 (0.66 to 0.97)	0.82 (0.65 to 1.03)	0.23	0.59
Diabetic (no. of events 92)	1.0	0.68 (0.35 to 1.31)	0.73 (0.38 to 1.42)	0.40 (0.15 to 1.02)	0.08	
Hypertension status						
Nonhypertensive (no. of events 828)	1.0	0.76 (0.61 to 0.95)	0.72 (0.57 to 0.90)	0.81 (0.61 to 1.06)	0.23	0.26
Hypertensive (no. of events 482)	1.0	0.82 (0.61 to 1.11)	0.95 (0.70 to 1.29)	0.73 (0.49 to 1.09)	0.29	
Alcohol consumption						
Abstainer (no. of events 346)	1.0	0.78 (0.56 to 1.08)	0.91 (0.66 to 1.25)	0.91 (0.61 to 1.38)	0.92	0.68
Drinker (no. of events 964)	1.0	0.78 (0.63 to 0.97)	0.75 (0.60 to 0.94)	0.74 (0.56 to 0.97)	0.06	

*Adjusted for the same variables as in Table 2 except for the stratification variable.

†The no. of stroke events may not sum up to the total no. because of missing values for the stratification variable.

Our findings for coffee consumption and stroke incidence are consistent with those of the Nurses' Health Study (NHS)⁷ and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study.⁸ Results from the NHS showed that women who consumed ≥4 cups of coffee per day had a significant 20% lower risk of total stroke than those who seldom (<1/month) drank coffee.⁷ In the ATBC Study of male smokers, the risk of cerebral infarction was 23% lower among men who consumed ≥8 cups of coffee per day compared with those who consumed <2 cups per day; no association was observed for intracerebral hemorrhage or subarachnoid hemorrhage.⁸ In contrast, in a small cohort study of 499 hypertensive and nonsmoking men (including 76 total stroke events), the risk of ischemic stroke was 2.1-fold higher for men who consumed 3 cups of coffee per day as compared with nondrinkers.⁹ Most cohort studies of coffee consumption in relation to stroke mortality among healthy women and men^{10,11} or among diabetics^{12,13} have found no association. However, in a cohort study of Japanese women and men, coffee consumption was significantly inversely associated with stroke mortality among men but not in women.¹⁴

In the NHS,⁷ there was a significant interaction between coffee consumption and smoking status in relation to stroke risk. In that study, coffee consumption was inversely associated with risk of total stroke among never and past smokers but not among current smokers.⁷ In our study, coffee consumption was nonsignificantly inversely associated with cerebral infarction among never and past smokers but was not associated with risk among current smokers; however, we observed no statistically significant interaction.

Potential mechanisms by which coffee consumption may reduce the risk of stroke include attenuation of subclinical

inflammation, reduction in oxidative stress, and improved insulin sensitivity. A recent clinical trial showed that high consumption of filtered coffee (≥8 cups/day) versus no consumption led to a significant decrease in serum concentrations of interleukin-18 and 8-isoprostane and a significant increase in adiponectin, total cholesterol, high-density lipoprotein cholesterol, and apolipoprotein A-I concentrations.⁴ Moreover, an observational study among women found that caffeinated coffee consumption was inversely associated with plasma concentrations of E-selectin (surface leukocyte adhesion molecules) and C-reactive protein (a marker of chronic low-grade inflammation) in diabetic women and that decaffeinated coffee consumption was inversely associated with C-reactive protein concentrations in healthy women.⁵ An inverse association between coffee consumption and C-reactive protein concentrations has also been observed in Japanese populations.^{17,18} In addition, habitual coffee consumption has been associated with higher insulin sensitivity.³

Strengths of this study include its prospective and population-based design and the almost complete follow-up of study participants by linkage with population-based Swedish registers. A limitation of this study is that coffee consumption was assessed using a self-administered questionnaire, which will inevitably lead to some measurement error and misclassification of exposure. Another limitation is that our assessment of medical history and other covariates was based on self-report, which is less reliable than clinical measurements. Furthermore, although we adjusted for major risk factors for stroke, we cannot rule out the possibility that our findings may be due to unmeasured or residual confounding. There was no dose-response relation between coffee consumption and risk of cerebral infarction; rather, the risk

seemed to be increased among women who consumed <1 cup of coffee per day. We cannot entirely exclude the possibility that women with low coffee consumption may be more likely to be exposed to another unknown risk factor for stroke. However, the association persisted after adjustment for other known stroke risk factors.

In summary, in this prospective study of Swedish women, low or no coffee consumption was associated with an increased risk of stroke. Additional prospective studies on coffee consumption and stroke incidence as well as mechanistic studies investigating possible effects of coffee consumption on cardiovascular risk factors are warranted.

Sources of Funding

This study was supported by research grant from the Swedish Council for Working Life and Social Research (FAS) and the Swedish Research Council for Infrastructure.

Disclosures

None.

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Abstract 1

여성에서의 커피 섭취와 뇌졸중 위험도

Coffee Consumption and Risk of Stroke in Women

Susanna C. Larsson, PhD; Jarmo Virtamo, MD; Alicja Wolk, DMSc

(Stroke. 2011;42:908-912.)

Key Words: coffee ■ epidemiology ■ prospective studies ■ stroke ■ women**배경과 목적**

이전 연구들에서 커피 섭취는 뇌졸중 발병 및 사망과 연관된 연관성을 보여 주지 않았다. 저자들은 Swedish Mammography Cohort에서 커피 섭취와 뇌졸중 발병의 연관성에 대하여 조사하였다.

방법

저자들은 1997년 당시 심혈관질환이나 암 병력이 없는 여성 34,670명을 전향적으로 추적 조사하였다. 커피 섭취는 1997년에 스스로 작성한 설문지를 통하여 평가하였다. 뇌졸중의 발생은 Swedish Hospital Discharge Registry에서 확인하였다.

결과

10.4년의 평균 추적 조사 기간 동안 1,680건의 뇌졸중이 확인되었으며, 그 중 1,310건은 뇌경색(cerebral infarction), 154

건은 뇌내출혈(intracerebral hemorrhage), 79건은 거미막하출혈(subarachnoid hemorrhage), 137건은 명시되지 않은 뇌졸중이었다. 다른 위험인자들을 보정한 후 커피 섭취는 통계적으로 유의하게 전체 뇌졸중, 뇌경색, 거미막하출혈의 위험도는 낮추었으나 뇌내출혈의 위험도를 낮추지 않았다. 커피 섭취량(하루 1컵 미만, 하루 1~2컵, 하루 3~4컵, 하루 5컵 이상)에 따른 전체 뇌졸중의 다변수 상대위험도는 각각 1.00, 0.78 (95% CI, 0.66~0.91), 0.75 (95% CI, 0.64~0.88), 0.77 (95% CI, 0.63~0.92; *P* for trend=0.02)이었다. 커피 섭취와 뇌경색의 연관성은 흡연 상태, 체질량지수, 당뇨병이나 고혈압 병력, 알코올 섭취에 의하여 변경되지 않았다.

결론

이러한 소견은 커피를 적게 섭취하거나 섭취하지 않는 것이 여성에서 뇌졸중의 위험도를 높인다는 것을 암시한다.