



Systematic Reviews and Meta- and Pooled Analyses

Coffee Consumption and Risk of Stroke: A Dose-Response Meta-Analysis of Prospective Studies

Susanna C. Larsson* and Nicola Orsini

* Correspondence to Dr. Susanna C. Larsson, 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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Coffee consumption has been inconsistently associated with risk of stroke. The authors conducted a meta-analysis of prospective studies to quantitatively assess the association between coffee consumption and stroke risk. Pertinent studies were identified by searching PubMed and Embase from January 1966 through May 2011 and by reviewing the reference lists of retrieved articles. Prospective studies in which investigators reported relative risks of stroke for 3 or more categories of coffee consumption were eligible. Results from individual studies were pooled using a random-effects model. Eleven prospective studies, with 10,003 cases of stroke and 479,689 participants, met the inclusion criteria. There was some evidence of a nonlinear association between coffee consumption and risk of stroke (P for nonlinearity = 0.005). Compared with no coffee consumption, the relative risks of stroke were 0.86 (95% confidence interval (95% CI): 0.78, 0.94) for 2 cups of coffee per day, 0.83 (95% CI: 0.74, 0.92) for 3–4 cups/day, 0.87 (95% CI: 0.77, 0.97) for 6 cups/day, and 0.93 (95% CI: 0.79, 1.08) for 8 cups/day. There was marginal between-study heterogeneity among study-specific trends ($I^2 = 12\%$ and $I^2 = 20\%$ for the first and second spline transformations, respectively). Findings from this meta-analysis indicate that moderate coffee consumption may be weakly inversely associated with risk of stroke.

coffee; meta-analysis; prospective studies; review; stroke

Abbreviation: CI, confidence interval.

Coffee is one of the most frequently consumed beverages worldwide. Because of the popularity of coffee, even small health effects of coffee could have considerable public health consequences. Compounds in coffee may have either beneficial or unfavorable effects on the cardiovascular system. The phenolic compounds in coffee possess antioxidant capacity and can inhibit the oxidative modification of low density lipoprotein cholesterol (1–3), thereby reducing the atherosclerotic process. On the other hand, regular intake of caffeine has been associated with increased blood pressure (4), and hypertension is a risk factor for cardiovascular disease (5, 6). Coffee consumption may also have effects on serum cholesterol and homocysteine concentrations, oxidation, and inflammation (7). Findings from a recent meta-analysis showed a nonlinear relation between coffee consumption and risk of coronary heart disease (8). While moderate coffee consump-

tion (1–3 cups/day in the United States or 3–4 cups/day in Europe) was associated with a significantly lower risk of coronary heart disease in women and in men and women followed for ≤ 10 years, no association was observed for heavy coffee consumption (8). Ample evidence also indicates that coffee consumption is inversely associated with risk of type 2 diabetes (9), which is a risk factor for cardiovascular disease. Whether coffee consumption affects the risk of stroke remains unclear. Results from prospective studies of the association between coffee consumption and stroke risk have not yet been summarized.

We conducted a meta-analysis of data from prospective studies to quantitatively assess the relation between coffee consumption and risk of stroke. We performed a dose-response meta-analysis to examine a potential nonlinear association between coffee consumption and stroke.

MATERIALS AND METHODS

Literature search and selection

We performed a literature search from January 1966 through May 2011 using the PubMed and Embase databases, with the key word *coffee* combined with *stroke*. The search was limited to studies carried out in humans. In addition, the reference lists of retrieved articles were scrutinized to identify further relevant studies. No language restrictions were imposed. We followed standard criteria for conducting meta-analyses and reporting the results (10).

Studies were eligible for inclusion in this meta-analysis if they met the following criteria: 1) the study had a prospective design; 2) the exposure of interest was coffee consumption; 3) the outcome was nonfatal and/or fatal stroke; and 4) the investigators reported relative risks with 95% confidence intervals for 3 or more quantitative categories of coffee consumption.

Data extraction

The following data were extracted from each study: first author's surname, publication year, study location, study period, duration (years) of follow-up, sex, age, sample size, stroke outcomes, coffee consumption categories, covariates adjusted for in the multivariable analysis, and relative risks (with their 95% confidence intervals) for all categories of coffee consumption. We extracted the relative risks that reflected the greatest degree of adjustment for potentially confounding variables. However, if results were reported for 2 multivariable models—one model that adjusted for potential intermediates of the coffee-stroke relation (e.g., hypertension and hypercholesterolemia) and another model that did not adjust for intermediates—we extracted the relative risks from the multivariable model that did not include the intermediates. Data extraction was conducted by 2 investigators, with disagreements being resolved by consensus.

For every study, the median or mean coffee consumption for each category was assigned to each corresponding relative risk. When the median or mean consumption per category was not reported in the article, we assigned the midpoint of the upper and lower boundaries in each category as the average consumption. If the upper boundary for the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. When the lowest category was open-ended, we set the lower boundary to zero.

Statistical analysis

We performed a 2-stage random-effects dose-response meta-analysis to examine a potential nonlinear relation between coffee consumption and stroke risk. This was done by modeling coffee consumption using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (11). In the first stage, a restricted cubic spline model with the 2 spline transformations (3 knots minus 1) was estimated using generalized least-squares regression taking into account the correlation within each set of published relative risks as described by Orsini et al. (12). In the second

stage, we combined the 2 regression coefficients and the variance/covariance matrix that had been estimated within each study, using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (13). The pooled relative risks for specific exposure values (cups of coffee per day) were estimated using a procedure described by Orsini and Greenland (14). A *P* value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero.

In separate analyses, we pooled the relative risks for comparable categories of coffee consumption as compared with the lowest category. In this approach, we combined the coffee consumption categories into 5 groups: reference (the lowest category in each study), <3 cups/day, 3–<5 cups/day, 5–<7 cups/day, and ≥7 cups/day.

Statistical heterogeneity among studies was assessed using the multivariate generalization of the I^2 statistic (13, 15). Two cutpoints of these I^2 values were considered, creating 3 groups: <30% (no between-study heterogeneity or marginal between-study heterogeneity), 30%–75% (mild heterogeneity), and >75% (notable heterogeneity). We conducted analyses stratified by study location, sex, years of follow-up, and stroke subtype. Publication bias was evaluated with Egger's regression test (16). All statistical analyses were conducted with Stata software (StataCorp LP, College Station, Texas). *P* values less than 0.05 were considered statistically significant.

RESULTS

Study characteristics

The search strategy identified 138 articles on humans, of which 124 articles were excluded after review of the title or abstract (Figure 1). Fourteen full-text articles were reviewed (17–30). One article that reported results for coffee consumption in relation to cardiovascular disease in a subgroup of diabetic patients (23) was excluded because data from this

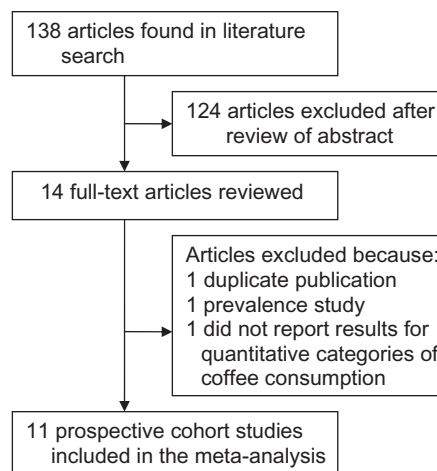


Figure 1. Selection of studies for inclusion in a meta-analysis of coffee consumption and stroke risk, 1966–2011.

cohort were reported in another publication with a larger sample size (including both nondiabetics and diabetics) (24). We further excluded a prevalence study (17) and 1 study that reported a relative risk estimate only for an increment of 3 cups/day (19). Thus, the meta-analysis included 11 independent prospective studies published between 1990 and 2011 (Table 1). Combined, these studies had 10,003 stroke cases and 479,689 study participants. Seven studies were conducted in Europe, 2 in the United States, and 2 in Japan. Two studies consisted of patients with a recent acute myocardial infarction (21, 25), and 1 study included diabetes patients only (20). The remaining 8 studies consisted of persons from the general population (no subgroups) who were free of cardiovascular disease or stroke at the start of follow-up. Most studies provided relative risk estimates that were adjusted for age (all 11 studies), smoking (all 11 studies), alcohol consumption (9 studies), history of diabetes (8 studies), body mass index (7 studies), history of hypertension or measured blood pressure (5 studies), physical activity (7 studies), and dietary factors other than total energy intake and tea consumption (7 studies).

Overall association between coffee consumption and stroke

We found some evidence of a nonlinear association between coffee consumption and stroke risk (P for nonlinearity = 0.005) (Figure 2). Compared with no coffee consumption, the pooled relative risks of total stroke were 0.92 (95% confidence interval (CI): 0.89, 0.96) for 1 cup of coffee per day, 0.86 (95% CI: 0.78, 0.94) for 2 cups/day, 0.83 (95% CI: 0.74, 0.92) for 3–4 cups/day, 0.87 (95% CI: 0.77, 0.97) for 6 cups/day, and 0.93 (95% CI: 0.79, 1.08) for 8 cups/day (Table 2). There was marginal between-study heterogeneity among study-specific trends, defined by the coefficients of the first ($I^2 = 12\%$) and second ($I^2 = 20\%$) spline transformations of coffee consumption. Egger's regression test provided no evidence of substantial publication bias ($P = 0.14$).

Exclusion of the 2 studies consisting of patients with a recent acute myocardial infarction (21, 25) and 1 study of diabetes patients (20) did not change the results materially (Table 2). We obtained similar results when we removed data points above 6 cups of coffee per day, and there was still evidence of a nonlinear relation between coffee consumption and stroke (P for nonlinearity = 0.001). When we pooled the relative risks for comparable categories of coffee consumption, the relative risks of stroke were 0.88 (95% CI: 0.86, 0.90) for <3 cups/day, 0.88 (95% CI: 0.77, 1.01) for 3–<5 cups/day, 0.87 (95% CI: 0.75, 1.02) for 5–<7 cups/day, and 0.93 (95% CI: 0.76, 1.12) for ≥ 7 cups/day.

Subgroup analyses

The associations between coffee consumption and risk of stroke were similar across geographic regions and years of follow-up (Table 2). Moreover, the associations were similar for men and women, although results for women were unstable because of few data points at high levels of coffee consumption. There was evidence of a nonlinear association between coffee consumption and stroke (P for nonlinearity

< 0.05) in all subgroups except Asians and women. Among the 4 studies that reported results for stroke subtypes (22, 24, 26, 30), the associations between coffee consumption and stroke risk were similar for ischemic stroke and hemorrhagic stroke, but results were statistically significant only for ischemic stroke (Table 2).

DISCUSSION

Findings from this meta-analysis of prospective studies indicate that moderate consumption of coffee may be weakly inversely associated with risk of stroke. Consumption of 1–6 cups of coffee per day was significantly inversely associated with risk of stroke, with the strongest association (17% lower risk) being observed for 3–4 cups/day. Heavy coffee consumption (≥ 7 cups/day) was not significantly associated with stroke risk. The associations were similar for ischemic stroke and hemorrhagic stroke, but only results for ischemic stroke were statistically significant.

Coffee is a complex mixture of biologically active substances that may have both beneficial and harmful effects on the cardiovascular system. The phenolic compounds in coffee, such as caffeic, ferulic, and *p*-coumaric acids, have a strong antioxidant activity and may reduce the oxidation of low density lipoprotein cholesterol (1–3). Moreover, habitual coffee consumption has been associated with higher insulin sensitivity (31), and several studies have found an inverse association between coffee consumption and blood concentrations of some inflammatory markers (32–35). On the other hand, caffeine in coffee may increase blood pressure, although results are inconsistent. In a meta-analysis of randomized controlled trials, Noordzij et al. (4) found that regular caffeine intake was positively associated with blood pressure. However, a large prospective study showed an inverse U-shaped relation between total caffeine intake and incident hypertension (36). In analysis of specific caffeinated beverages, consumption of cola but not coffee was associated with an increased risk of hypertension (36), suggesting that compounds in coffee other than caffeine might be protective. Results from a meta-analysis of randomized controlled trials showed that consumption of caffeinated and boiled coffee was associated with increased total and low density lipoprotein cholesterol concentrations (37). Findings from the present meta-analysis suggest that at moderate to high levels of consumption, the beneficial effects of coffee overcome the potentially unfavorable effects.

A strength of this meta-analysis was the prospective design of the included studies, which should have eliminated the selection bias and recall bias that could be of concern in retrospective case-control studies. Moreover, many studies in this meta-analysis had a large sample and a long duration of follow-up. The large number of total cases provided high statistical power with which to quantitatively assess the relation between coffee consumption and stroke risk. The relatively large number of studies enabled us to conduct subgroup analyses according to study location and sex. Although evidence from long-term randomized trials is ideal, these studies are difficult to implement on a practical basis, especially for an exposure such as coffee consumption.

Table 1. Characteristics of Prospective Studies of Coffee Consumption and Stroke Risk Included in a Meta-Analysis, 1966–2011

First Author, Year (Reference No.)	Country and Study Period	Mean Duration of Follow-up, years	Sex	Age Range, years	No. of Stroke Cases	Sample Size, no.	Coffee Consumption Categories	Adjusted Relative Risk	95% Confidence Interval	Adjustment Factors
Grobbbee, 1990 (18)	United States, 1986–1988	2	Men	40–75	54 nonfatal and fatal	45,589	None <1 cup/day 2–3 cups/day ≥4 cups/day	1.00 0.58 0.68 0.48	Reference 0.25, 1.36 0.36, 1.31 0.18, 1.31	Age, smoking, BMI, history of diabetes, family history of MI, specific health profession, alcohol consumption, and intake of cholesterol, saturated fat, monounsaturated fat, polyunsaturated fat, and energy
Bidel, 2006 (20)	Finland, 1972–2003	20.8	Men and women	25–74	210 fatal	3,837 ^a	0–2 cups/day 3–4 cups/day 5–6 cups/day ≥7 cups/day	1.00 0.79 0.66 0.94	Reference 0.51, 1.22 0.43, 1.03 0.58, 1.52	Age, sex, education, study year, smoking, and alcohol and tea consumption
Silletta, 2007 (21)	Italy, 1993– 1998	3.3	Men and women	NA	119 nonfatal	11,231 ^b	Almost never <2 cups/day ≥2 cups/day	1.00 1.20 1.06	Reference 0.78, 1.85 0.64, 1.74	Age, sex, smoking, time from MI to enrollment, prior MI before index MI, BMI, history of hypertension, history of diabetes, peripheral vascular disease, electrical instability, results of exercise stress testing, left ventricular ejection fraction, New York Heart Association class, Canadian Cardiovascular Society angina symptoms, revascularization procedures, intake of n-3 polyunsaturated fatty acids, vitamin E use, antiplatelet agent use, angiotensin- converting enzyme inhibitor use, lipid- lowering medication use, β-blocker use, and intake of cooked vegetables, raw vegetables, fruit, fish, olive oil, other oil, butter, cheese, and wine
Larsson, 2008 (22)	Finland, 1985–2004	13.6	Men	50–69	3,281 nonfatal and fatal	26,556	<2 cups/day 2–3 cups/day 4–5 cups/day 6–7 cups/day ≥8 cups/day	1.00 ^c 0.91 0.88 0.77 0.77	Reference 0.79, 1.06 0.77, 1.02 0.66, 0.90 0.66, 0.90	Age, supplementation group, number of cigarettes smoked daily, BMI, systolic and diastolic blood pressure, serum total and high density lipoprotein cholesterol, histories of diabetes and coronary heart disease, leisure-time physical activity, and alcohol and tea consumption
Lopez-Garcia, 2009 (24)	United States, 1980–2004	24	Women	30–55	2,280 nonfatal and fatal	83,076	<1 cup/month <4 cups/week 5–7 cups/week 2–3 cups/day ≥4 cups/day	1.00 0.98 0.88 0.81 0.80	Reference 0.84, 1.15 0.77, 1.02 0.70, 0.95 0.64, 0.98	Age, smoking, BMI, physical activity, menopausal status, use of hormone replacement therapy, aspirin use, glycemic load, and intake of whole grains, fruits, vegetables, fish, alcohol, calcium, potassium, sodium, folate, and energy
Mukamal, 2009 (25)	Sweden, 1992–2001	6.9–9.9	Men and women	45–70	135 nonfatal	1,643 ^b	<1 cups/day 1–<3 cups/day 3–<5 cups/day 5–<7 cups/day ≥7 cups/day	1.00 1.08 0.94 1.17 0.74	Reference 0.57, 2.02 0.49, 1.78 0.59, 2.29 0.31, 1.75	Age, sex, education, smoking, history of diabetes, obesity, physical inactivity, and consumption of alcohol, tea, and boiled coffee

Sugiyama, 2010 (26)	Japan, 1990–2001	10.3	Men and women	40–64	191 fatal	37,742	<i>Men</i>			Age, sex, education, smoking, BMI, histories of hypertension and diabetes, daily walking time, energy intake, and consumption of alcohol, green tea, oolong tea, black tea, rice, miso soup, meat, dairy products, fish, vegetables, and fruits
							Never	1.00	Reference	
							Occasionally	1.51	0.89, 2.57	
							1 cup/day	1.06	0.60, 1.87	
							<i>Women</i>			
							Never	1.00	Reference	
Leurs, 2010 (27)	Netherlands, 1986–1996	10	Men and women	55–69	708 fatal	120,852	<i>Men</i>			Age, smoking, number of cigarettes smoked per day, years of active smoking, and energy intake
							<2 cups/day	1.00	Reference	
							>2–4 cups/day	0.84	0.60, 1.18	
							>3–6 cups/day	0.72	0.50, 1.04	
							>6 cups/day	1.15	0.74, 1.77	
							<i>Women</i>			
de Koning Gans, 2010 (28)	Netherlands, 1993–2006	13	Men and women	20–69	563 nonfatal and 70 fatal	37,514	<1 cup/day	1.00	Reference	Age, sex, cohort (strata), education, physical activity, smoking, waist circumference, menopausal status, and intake of alcohol, tea, saturated fat, dietary fiber, vitamin C, and energy
							1–2 cups/day	1.13	0.84, 1.53	
							2.1–3 cups/day	1.16	0.86, 1.57	
							3.1–4 cups/day	1.06	0.80, 1.41	
							4.1–6 cups/day	1.15	0.88, 1.50	
							>6 cups/day	1.21	0.87, 1.67	
Mineharu, 2011 (29)	Japan, 1988–2003	13.1	Men and women	40–79	782 fatal	76,979	<i>Men</i>			Age, smoking, BMI, histories of hypertension and diabetes, education, hours of walking per day, hours of sports participation per week, perceived mental stress, multivitamin use, vitamin E supplement use, energy intake, and consumption of alcohol, fruits, vegetables, beans, meat, fish, and seaweed
							<1 cup/week	1.00	Reference	
							1–6 cups/week	0.78	0.50, 1.20	
							1–2 cups/day	0.67	0.47, 0.96	
							≥3 cups/day	0.45	0.17, 0.87	
							<i>Women</i>			
Larsson, 2011 (30)	Sweden, 1998–2008	10.4	Women	49–83	1,680 nonfatal	34,670	<1 cup/day	1.00	Reference	Age, education, smoking, BMI, physical activity, histories of diabetes and hypertension, aspirin use, family history of MI, energy intake, and consumption of alcohol, red meat, fish, fruits, and vegetables
							1–2 cups/day	0.78	0.66, 0.91	
							3–4 cups/day	0.75	0.64, 0.88	
							≥5 cups/day	0.77	0.63, 0.92	

Abbreviations: BMI, body mass index; MI, myocardial infarction; NA, not available.

^a Patients with diabetes.

^b Patients with a recent acute MI.

^c Relative risks are for ischemic stroke.

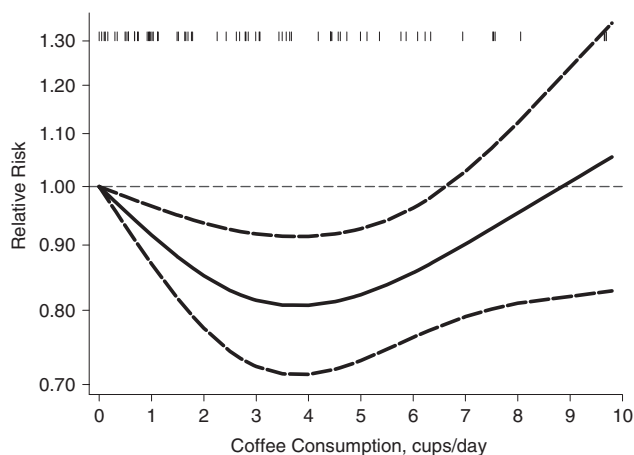


Figure 2. Adjusted relative risk of stroke associated with coffee consumption in a meta-analysis of published studies, 1966–2011. Coffee consumption was modeled with restricted cubic splines in a multivariate random-effects dose-response model. The lowest value of zero was used to estimate all relative risks. Tick marks above the curve represent the positions of the published relative risks. The vertical axis is on a log scale.

Our meta-analysis also had several potential limitations. First, because of the observational design, exclusion of potential confounding from other stroke risk factors cannot be ruled out. A meta-analysis is not able to address problems with confounding factors that could be inherent in the original studies. However, in most studies included in this meta-analysis, the investigators had adjusted for major potential confounders, including age, smoking, body mass index, physical activity, histories of diabetes and hypertension, alcohol consumption, and dietary factors. The weaker and nonsignificant inverse association between coffee and stroke risk at higher levels of coffee consumption could potentially be due to residual confounding from unhealthy behaviors related to high coffee consumption, such as cigarette smoking.

Another limitation is misclassification of coffee consumption, which was inevitable given that consumption was self-reported and only 1 study (24) updated information on coffee consumption during follow-up. Nevertheless, results from validation studies indicated that coffee consumption was assessed with relatively high validity. The correlations between coffee consumption assessed by questionnaire and consumption assessed by diet records were 0.78 in US women (24), 0.72 in Finnish men (22), 0.6 in Swedish women (30), and 0.70 in Japanese men and women (26). Misclassification of coffee consumption due to measurement error or changes in consumption during follow-up would most likely lead to underestimation of the true association between coffee consumption and stroke risk. Hence, the association between coffee consumption and risk of stroke may be even stronger.

Third, heterogeneity among studies may have been introduced because of consumption of different types of coffee (e.g., caffeinated vs. decaffeinated coffee), different methods of coffee preparation (e.g., filtered, boiled, espresso), and differences in serving size and brew strength. Two studies

reported results for both caffeinated and decaffeinated coffee. In the Health Professionals Follow-up Study, consumption of caffeinated coffee was inversely associated with stroke (for ≥ 4 cups/day vs. none, relative risk = 0.28, 95% CI: 0.06, 1.26) but consumption of decaffeinated coffee was not (corresponding relative risk = 1.16, 95% CI: 0.26, 5.10) (18). In the Nurses' Health Study, both caffeinated and decaffeinated coffee were nonsignificantly inversely associated with risk of stroke (24). Different genotypes and gene-environment interactions may also partially account for the variations in associations between coffee consumption and stroke risk among studies. For example, caffeine metabolism is slower in Japanese persons than in Western populations (38). Finally, in a meta-analysis of data from published studies, publication bias could be of concern. Although we found no statistically significant evidence for publication bias, we cannot exclude the possibility that publication bias may have affected the results.

Two studies could not be included in the present dose-response meta-analysis (17, 19). One of those studies consisted of 499 hypertensive men, of whom 76 developed stroke (55 thromboembolic strokes and 13 hemorrhagic strokes) during a mean follow-up period of 14.8 years (19). In that study, coffee consumption was positively associated with risk of thromboembolic stroke (P for trend = 0.006) but not with hemorrhagic stroke (19). The reason for the observed positive association is unclear, but it may be due to the inclusion of only hypertensive men, to the very small sample size, or to confounding from unhealthy behaviors among men with high coffee consumption. In the other study, Heyden et al. (17) found that stroke deaths were more frequent in white and black men who reported low lifetime coffee consumption, whereas white and black women who were heavy consumers of coffee had slightly higher age-adjusted stroke mortality than their counterparts who were low consumers or nondrinkers.

In summary, results from this meta-analysis indicate that moderate coffee consumption may be weakly inversely associated with risk of stroke. It is unclear whether the lack of a linear dose-response relation between coffee consumption and stroke is due to potentially unfavorable effects of coffee at higher consumption levels or is due to residual confounding from other stroke risk factors related to coffee consumption. Future studies should attempt to assess whether this association is causal and whether the relation differs by stroke subtype or is modified by polymorphisms in genes encoding enzymes involved in the metabolism of compounds in coffee.

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Author affiliations: Division of Nutritional Epidemiology, National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Susanna C. Larsson, Nicola Orsini); and Unit of Biostatistics, National Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (Nicola Orsini).

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Table 2. Adjusted Relative Risk of Stroke Associated With Consumption of 1–8 Cups of Coffee per Day in Comparison With No Consumption (Reference Group), by Study Location, Sex, Duration of Follow-up, and Stroke Subtype, 1966–2011

	No. of Studies	Coffee Consumption, cups/day															
		1		2		3		4		5		6		7		8	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
All studies	11	0.92	0.89, 0.96	0.86	0.78, 0.94	0.83	0.74, 0.92	0.83	0.74, 0.92	0.84	0.75, 0.94	0.87	0.77, 0.97	0.90	0.79, 1.02	0.93	0.79, 1.08
Exclusion of 3 studies ^a	8	0.91	0.89, 0.93	0.85	0.82, 0.88	0.82	0.78, 0.86	0.82	0.76, 0.88	0.84	0.77, 0.92	0.88	0.79, 0.98	0.92	0.82, 1.05	0.97	0.84, 1.12
Study location																	
Europe	7	0.93	0.88, 0.98	0.88	0.80, 0.96	0.85	0.76, 0.95	0.85	0.76, 0.95	0.86	0.77, 0.97	0.89	0.78, 1.00	0.91	0.79, 1.05	0.94	0.80, 1.11
United States	2	0.91	0.90, 0.93	0.85	0.82, 0.87	0.81	0.76, 0.86	0.79	0.70, 0.89								
Japan	2	0.79	0.64, 0.97	0.72	0.50, 1.03	0.84	0.20, 3.57										
Sex																	
Men	5	0.90	0.83, 0.98	0.83	0.73, 0.96	0.80	0.68, 0.94	0.80	0.68, 0.94	0.81	0.70, 0.95	0.84	0.71, 0.99	0.87	0.71, 1.07	0.91	0.70, 1.18
Women	5	0.87	0.78, 0.97	0.84	0.74, 0.95	0.95	0.67, 1.34	1.24	0.52, 3.00	1.81	0.37, 8.90						
Both sexes	4	0.97	0.87, 1.09	0.95	0.78, 1.17	0.95	0.75, 1.21	0.96	0.75, 1.23	0.98	0.77, 1.25	1.01	0.79, 1.28	1.03	0.78, 1.45	1.06	0.78, 1.45
Duration of follow-up, years																	
≤10	4	0.89	0.80, 0.98	0.81	0.68, 0.97	0.79	0.64, 0.97	0.81	0.66, 1.00	0.86	0.70, 1.07	0.94	0.73, 1.22	1.04	0.75, 1.44	1.14	0.75, 1.73
>10	7	0.93	0.89, 0.97	0.88	0.81, 0.95	0.85	0.77, 0.94	0.84	0.75, 0.94	0.85	0.76, 0.95	0.86	0.76, 0.97	0.88	0.76, 1.01	0.89	0.76, 1.05
Stroke subtype																	
Ischemic	4	0.92	0.87, 0.98	0.87	0.79, 0.96	0.84	0.75, 0.93	0.82	0.74, 0.91	0.82	0.74, 0.90	0.82	0.72, 0.92	0.82	0.70, 0.96	0.82	0.67, 1.00
Hemorrhagic	4	0.92	0.82, 1.03	0.86	0.70, 1.06	0.84	0.65, 1.08	0.83	0.63, 1.10	0.84	0.63, 1.14	0.86	0.63, 1.17	0.87	0.62, 1.22	0.89	0.62, 1.28

Abbreviations: CI, confidence interval; RR, relative risk.

^a Exclusion of 2 studies of patients with recent acute myocardial infarction (21, 25) and 1 study of diabetes patients (20).

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