

Green and Black Tea Consumption and Risk of Stroke

A Meta-Analysis

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Background and Purpose—Experimental models of stroke provide consistent evidence of smaller stroke volumes in animals ingesting tea components or tea extracts. To assess whether a similar association of black or green tea consumption with reduced risk is evident in human populations, we sought to identify and summarize all human clinical and observational data on tea and stroke.

Methods—We searched PubMed and Web of Science for all studies on stroke and tea consumption in humans with original data, including estimation or measurement of tea consumption and outcomes of fatal or nonfatal stroke. Data from 9 studies involving 4378 strokes among 194 965 individuals were pooled. The main outcome was the occurrence of fatal or nonfatal stroke. We tested for heterogeneity and calculated the summary effect estimate associated with consumption of ≥ 3 cups of tea (green or black) per day using random-effects and fixed-effects models for the homogeneous studies. Publication bias was also evaluated.

Results—Regardless of their country of origin, individuals consuming ≥ 3 cups of tea per day had a 21% lower risk of stroke than those consuming < 1 cup per day (absolute risk reduction, 0.79; CI, 0.73 to 0.85). The proportion of heterogeneity not explained by chance alone was 23.8%.

Conclusions—Although a randomized clinical trial would be necessary to confirm the effect, this meta-analysis suggests that daily consumption of either green or black tea equaling 3 cups per day could prevent the onset of ischemic stroke. (*Stroke*. 2009;40:1786-1792.)

Key Words: black tea ■ *Camelia sinensis* ■ green tea ■ ischemic stroke ■ theophylline

Globally, cerebrovascular disease causes an estimated 5.4 million deaths per year.¹ Stroke can have a profound influence on the individual and their families.² Survivors frequently experience hemiparesis, aphasia, hemianopia, depressive symptoms, dysphagia, incontinence, and difficulty walking.³ Among noninstitutionalized survivors, stroke has a significant impact on quality of life, including mental health, physical health, and subjective perceptions of health.⁴ The occurrence of stroke is estimated to be \$62.7 billion in 2007 in the United States due to lost productivity, hospital and nursing home costs, or \$140 000 per victim.⁵ The cost of stroke between 2005 and 2050 in the United States is estimated to exceed \$2 trillion.⁶

There are few known preventive strategies to date. Cigarette smoking, hypertension, and diabetes mellitus are the known actionable risk factors. In a few studies, physical activity appeared to be associated with lower risk of stroke by approximately 20%.^{7,8} Preventive approaches have been shown to powerfully impact disease burden as well as costs.^{9,10}

We have previously conducted meta-analyses of the relationship between *Camelia sinensis* consumption as black tea and cardiovascular disease risk, which suggested heterogeneity of results and associated with an overall reduced risk.¹¹ At

that time, little data on stroke in human populations were available, but the available information, although inadequate for a meta-analysis, was suggestive of an association with reduced risk. Further evidence supportive of this hypothesis comes from preclinical studies in which stroke was induced in rats, mice, and gerbils. In these experiments, either epigallocatechin gallate^{12–14} or tea catechin extracts were given in doses ranging from 25 to 50 mg/kg intraperitoneally to rats subjected to cerebral arterial occlusion. They found reduced brain infarct area and stroke volume in an inverse dose-dependent fashion. Where studied, neurological deficits were found to be significantly alleviated among the rats provided with the catechins.¹⁵ The authors of that study concluded that “daily intake of green tea catechins efficiently protects the penumbra from irreversible damage due to cerebral ischemia, and consequent neurological deficits.” Treatment of gerbils, in which ischemia was induced by occlusion of the right common carotid artery for 30 to 90 minutes, with 50 mg/kg epigallocatechin gallate, reduced the formation of postischemic brain edema and infarct volume.¹⁶ Green tea extract functioned similarly in this species.¹⁴

This study was undertaken to rigorously examine the human clinical and epidemiological data available to deter-

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mine whether, within the mix of other contributing factors, self-selected consumption of black or green tea as an infused hot beverage has an impact on the risk of stroke in humans. To examine this, we conducted a systematic literature review and meta-analysis of all unearthed human data on tea consumption and stroke.

Methodology

Eligibility Criteria

Inclusion criteria were established in advance of the search. The search strategy was set to include both clinical trials and observational epidemiological studies. No studies with original data on stroke as a primary or secondary outcome in humans and its association to tea consumption were excluded. Authors of studies published on tea effects that mentioned stroke but did not provide data were contacted to request the data necessary to include them in the meta-analysis.

Search Strategy

To identify the studies of interest, we conducted an electronic search of the PubMed and Web of Science databases through October 2007. MeSH terms were used and were exploded for narrower subjects and text words related to tea (tea, theophylline, *Camelia sinensis*, coffee, coffea, or caffeine) as well as the search terms “tea,” “green tea,” “black tea,” “flavonoids,” “*Camelia sinensis*,” and “stroke” (text words included cerebrovascular accident, brain ischemia, intracranial hemorrhages, and cerebral hemorrhage) and search terms “subarachnoid hemorrhage,” “ischemic stroke,” “hemorrhagic stroke.” The study was limited to human subjects. Reviews were excluded. No language restrictions were made. A University of California at Los Angeles research librarian (R.O.) conducted an independent search of the same terms to ensure that the search was comprehensive. The reference lists of the relevant articles were reviewed to identify any citations that might be related to original human studies on stroke and tea. In studies in which estimates were not quantified, the authors were contacted to request the numeric estimates. The interim literature was assessed for additional publications. One additional study was identified in June 2008 and added to the analysis.¹⁷ The search was conducted once more in September 2008 with 2 terms added (catechin and cerebral infarction) to ensure comprehensiveness.

Data Reviews and Statistical Analysis

Two reviewers independently reviewed all of the resulting abstracts for applicability (L.A. and A.W.). The titles and abstracts were reviewed to identify those that were relevant and contained any original data in human populations. Inconsistencies were resolved through discussion until a consensus was reached. Data were extracted using a standardized spreadsheet.

Relative risk or risk ratio was used as the primary effect estimate. This meta-analysis addresses studies in which the outcome was relative risk of stroke. The STATA (Version 10) module GSLT was used to estimate the risk ratio and 95% confidence limits for 3 cups per day. StatsDirect (Version 2.6.6) was used to find the fixed-effect model estimates and random-effect model estimates for different combinations of studies.

We assessed the presence of between-study heterogeneity in 2 main ways: by using forest plots to see how well the confidence intervals overlap and using Hedge's Q test.¹⁸ The test of heterogeneity was considered significant if $P < 0.10$. The I^2 index¹⁹ (range, 0% to 100%) was also calculated to measure the degree of inconsistency in the studies' results. It describes the percentage of variation in the estimates of tea effect that is due to heterogeneity between the studies.

A pooled risk ratio with 95% CIs was calculated across homogeneous studies. The pooled risk ratios were estimated using both fixed- and random-effect models.²⁰ When fixed-effect and random-effect meta-analyses gave identical results, it is unlikely that there was important statistical heterogeneity and the fixed-effect models

were presented as the primary outcome. If, however, results varied across studies, the more conservative option, to use the random-effect model estimates was undertaken.

The risk estimates used are based on the relative risk of a ≥ 3 cup per day increase in tea consumption for most studies. For these, inverse variance-weighted, categorical regression was used to estimate linear exposure-response curves from the reported categories of consumption using the covariance-corrected method of Greenland and Longnecker as reported previously.²¹ STATA Version 10 GSLT was used to estimate the risk ratios and confidence limits for 3 cups per day across the reported dose levels. StatsDirect Version 2.6.6 was used to determine estimates from both fixed- and random-effects models for different combinations of studies.

Exposure values, in cups per day, were estimated for the tea consumption categories in the original studies as described in our earlier publication.¹¹ In brief, if medians or means were available for the tea consumption categories, they were used. Otherwise, category midranges were applied, and for open-ended response levels, 1.2 times the previous category was applied with one exception in which, because of skewness a factor, 1.4 times the lower boundary was applied.

Subgroup analyses were also performed according to the type of tea (green/black), study type (cohort only), and the study countries (Asian/non-Asian). Publication bias was evaluated using the funnel graph, the Egger regression method,²² and the rank correlation method of Begg.²³

To investigate the impact of various study characteristics on the study estimates of risk ratio, metaregression analysis was conducted. The natural logarithm of the risk ratio was the dependent variable; the number of participants, the number of cancer cases, the type of tea, and the geographic location were explanatory factors. Weighted linear regression analysis was conducted weighted to the inverse of the variance of the logarithm of the risk ratio. Univariable linear regression was run for each factor first. Then, all factors were included for a multivariable regression with a backward stepwise approach to select the significant ones.

All tests were conducted without prior assumption of a protective effect and thus were 2-tailed. The meta-analysis was performed using Statsdirect Statistical Software Version 2.6.6.²⁴

Results

The search through PubMed yielded 59 citations, including one in Chinese that was translated by a Chinese national (W.L.). Screening of these citations for original human studies resulted in the identification of 11 studies; 8 cohorts, 2 case-controls, and one cross-sectional study that could provide original data on some type of stroke in relationship to tea consumption. A few studies were identified that associated flavonoid intake with stroke but did not have separate estimates for tea consumption and were therefore not included.

Ten studies from 6 different countries contributed to the meta-analysis: China, Japan, Finland, The Netherlands, Australia, and the United States. Mortality from stroke among 35- to 74-year-old men in these countries ranged from a low of 30 per 100 000 in Australia to a high of 243 per 100 000 men living in rural China. Finland and Japan had intermediary mortality rates of 54 and 66, respectively.⁵ The end points for the study included and combined both fatal and nonfatal stroke. All of the cohorts provided stroke mortality data to which the cohort studies of Hirvonen²⁵ and Keli²⁶ also included nonfatal strokes. The case-control and cross-sectional studies included incidence and prevalence of stroke. Many of the studies had risk estimates for total strokes and one or more breakdowns for ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage. One study²⁷ included only subjects with an intracerebral hemorrhage and another

Table 1. Overview of Observational Epidemiological Studies of the Effect of Tea Consumption on Stroke

Study	Country	Population	Tea	Outcome	RR 3 cups/day*	95% CI of RR	Follow-up, years	All Subjects	Cases	Weights (1/SE ²)	Percent \geq n cup/day†
Cohort studies											
Larsson ¹⁷	Finland	Men	Black	Stroke Both	0.75	0.64–0.88	13.6	26 556	2702	18.5	22.4% \geq 0.5 cup/day
Kuriyama ³⁴	Japan	Men	Green	Stroke Fatal	0.85	0.73–0.99	7	19 060	249	13.9	59.6% \geq 1 cup/day
		Women	Green	Stroke Fatal	0.80	0.69–0.92	7	21 470	223	12.0	77.2% \geq 1 cup/day
Sesso ^{43‡}	United States	Women	Black	Stroke Both	0.91	0.61–1.37	7	37 902	256	1.4	34.2% \geq 1 cup/day
Hirvonen ²⁵	Finland	Men	Black	Stroke Both	0.71§	0.38–1.35	6	26 415	736	1.8	17.7% \geq 0.7 cup/day
Yochum ⁴⁴	United States	Women	Black	Stroke Fatal	0.73	0.38–1.41	10	34 492	131	5.5	25.0% \geq 0.7 cup/day
Keli ²⁶	Netherlands	Men	Black	Stroke Both	0.34	0.17–0.69	15	552	42	4.9	75.7% \geq 1.4 cup/day
Klatsky ⁴⁵	United States	Both	Black	Stroke Fatal	0.84	0.64–1.10	8	12 893	275	18.4	19.4% \geq 1 cup/day
Sato ⁴⁶	Japan	Women	Green	Stroke Fatal	0.68	0.56–0.82	4	14 360	174	24.3	81.9% \geq 1 cup/day
Case-control studies											
Thrift ²⁷	Australia	Both	Black	CH nonfatal	1.51	0.89–2.56		662	331		67.1% \geq 1 cup/day
Okamoto ²⁸	Japan	Both	Green	SAH	0.56	0.32–0.98		603	201		70.9% \geq 1 cup/day
Cross-sectional											
Chen ⁴⁷	China	Both	Both	Stroke	0.95	0.72–1.25	0	14 212	160	13.8	38.5% \geq 1 cup/day
			Green		0.35	0.18–0.72		1877	9		
			Black		0.24	0.06–1.01		2843	48		

*Relative risk for drinking 3 cups/day versus drinking no tea unless otherwise specified.

†Percent of subjects who drink at least given no. of cups per day (in case-control study only for control subjects).

‡Dr Sesso provided additional data to allow calculations of the risk for 3 cups on the same population.

§Relative risk for \geq 1 cup (170 mL/d) versus $<$ 1 cup/day.

RR indicates rate ratio; CH, cerebral hemorrhage; SAH, subarachnoid hemorrhage.

only included subarachnoid hemorrhage.²⁸ Because these are minority subsets of total stroke incidence, neither study was included in the meta-analysis, leaving only one case-control study in the analysis.

Three of the studies included only women and 3 only men. For 3 studies, the effect estimates were presented only as combined across both gender groups. One study presented risk estimates separately for men and women. In that case, both estimates were included separately in the analyses. Some of the studies excluded smokers; others attempted to control for smoking in the analyses. These studies included 7 populations that drank primarily or exclusively black tea and 3 that drank primarily green tea. The studies are presented in Table 1.

As seen in the table and the summary meta-analysis plot presented as Figure 1, all of the eligible studies had risk point estimates <1.0 . The fixed- and random-effect model estimates from the meta-analyses were extremely similar and both are presented. Although there are a relatively small number of studies identified, and none of them were clinical trials testing the effect of tea, the meta-analytic model was quite robust. The confidence intervals were narrow and there was no significant heterogeneity. The Q value for the meta-analysis involving 10 studies was 11.8. The I^2 for the 10 studies in total was 23.8%. There was surprisingly no indication of significant publication bias on the topic, although an outlier can be seen in the funnel plot presented in Figure 1. The Forrest plot for these 10 studies along with the meta-analytic results are presented in Figure 2.

This meta-analysis combines different stroke end points, different types of tea consumption, and different study types.

To see if more homogeneous combinations came to different analyses, we conducted the meta-analysis in 5 subsets. The set of studies that included only green tea consumption included only 3 studies, and this combination of studies showed significant heterogeneity ($P=0.193$). A subset of Asian-only analyses in which black tea estimates were included was not significantly heterogeneous. The overall results from these subgroup analyses showed effect estimates that were all very similar to the overall effect estimate. That is, the strong association of tea consumption with reduced risk could not be attributed to an effect in Asians more than non-Asians or green tea consumers more than black tea consumers. The confidence intervals, even for the random-effect models, were all <1.0 , and the ranges, 0.64 to 0.94 seen in Table 2, were statistically significant.

Discussion

Despite different drinking customs and a broad range in risk of death due to stroke, across the 6 countries studied, a consistent association is found. The pooled meta-analyses show tea consumption to be associated with reduced risk for occurrence of and mortality from stroke. Subjects drinking ≥ 3 cups of tea per day appear to reduce risk of a fatal or nonfatal stroke by approximately 21% as compared with nondrinkers of tea. The effect does not appear to be specific to green or black tea or to Asian or non-Asian populations. These findings suggest that tea drinking may be one of the most actionable lifestyle changes to significantly reduce the risk of stroke.

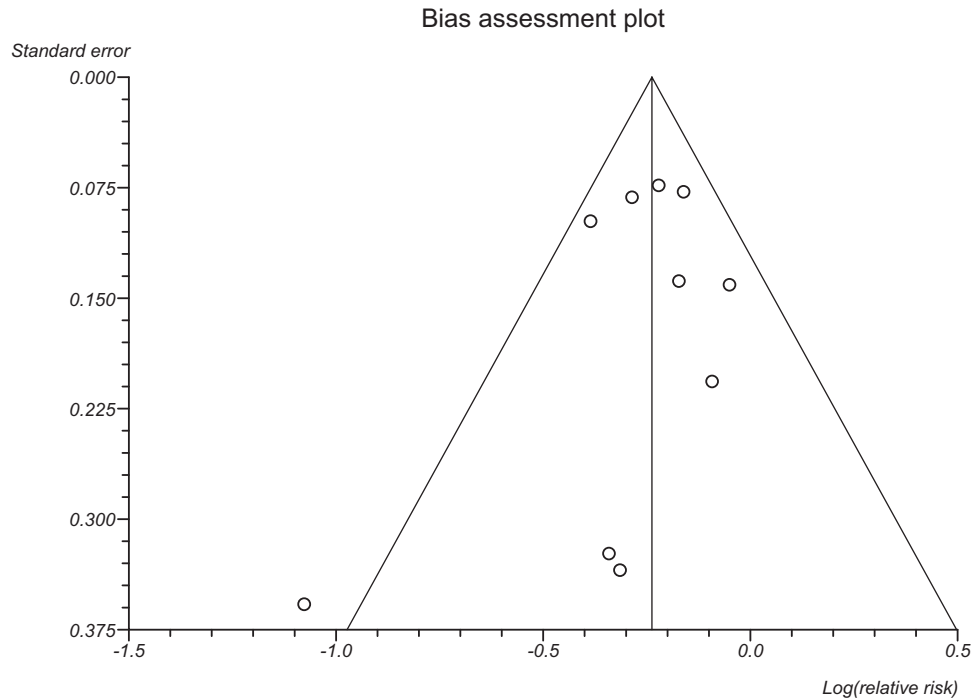


Figure 1. Funnel plot of studies of stroke and tea consumption.

The term “stroke” is used in this article despite its imprecision, because it was the outcome most commonly reported on in the epidemiological literature. More desirable would be the incorporation of a more exact diagnosis of the stroke subtype and mechanism (small versus large vessel, secondary to atheroma or dissection) based on brain imaging results as currently recommended,²⁹ which would allow a better understanding of the mechanism of action. However, this is not available currently in population-based studies. In the Western world, the majority of strokes are caused by cerebral ischemia; in Asia, they have historically been more commonly hemorrhagic in origin.

Our meta-analysis is consistent with animal research demonstrating that active ingredients in *Camelia sinensis* can reduce the damage associated with cerebrovascular accidents cited at the beginning of this article. It is also consistent with earlier findings of an association with reduced risk among drinkers of black tea on cardiovascular disease risk in general, although the findings from those studies were highly heterogeneous. In contrast, these stroke findings are remarkably homogeneous, suggesting a more consistent effect, a more homogeneous condition, and perhaps fewer competing mechanisms contributing to the etiology.

The results are consistent across green and black tea. Although, due to their processing difference, the types of catechins differ between green and black tea; their total amounts are comparable because both black and green tea are derived from the same source: the catechins produced within the *Camelia sinensis* plant.³⁰ The findings presented may seem surprisingly consistent across green and black tea, but both have demonstrated effects on vascular function.^{31,32}

This meta-analysis is potentially limited by the small number of studies. However, the total observational pool encompassed 194 965 individuals and 4378 stroke events.

Furthermore, because the weight of the meta-analysis stems from the cohort studies, there is little cause for concern that recall bias may be contributing to the findings. However, there is random measurement error inherent in measurement of the exposure of interest, cups of tea. Ideally, dry tea matter would be assessed and the differences in tea concentration in different countries taken into account. When we have gone to those lengths in a study of tea, the risk estimates became stronger.³³

As always the case in meta-analyses, the results are susceptible to publication bias such that studies showing an effect are more likely to be published. However, in most of the epidemiological studies, unlike the cited animal studies, stroke was not the primary outcome of interest. The studies addressed total mortality or cardiovascular disease mortality or incidence in relation to tea consumption. Because of this, there is a lower likelihood of publication bias regarding the stroke events if not the primary events. In fact, 5 of the contributing studies showed nonsignificant relationships between tea consumption and stroke, 3 of which had very large confidence intervals.

Ideally, stroke as an outcome would be separated into different subcategories without combining ischemic stroke and hemorrhagic stroke. This would be particularly interesting because animal evidence suggests that tea consumption may reduce the damage of ischemic stroke but increase the risk of hemorrhagic.¹⁶ However, most of the studies combine all strokes, and the few addressing strictly subarachnoid hemorrhage and hemorrhagic stroke are too limited to meta-analyze. Furthermore, the 3 studies that break out nonischemic stroke have too few cases to provide robust estimates. Two of these were Finnish studies, one¹⁷ of which had 267 ischemic strokes and only 41 hemorrhagic strokes; in the other study,²⁵ only 95 of the

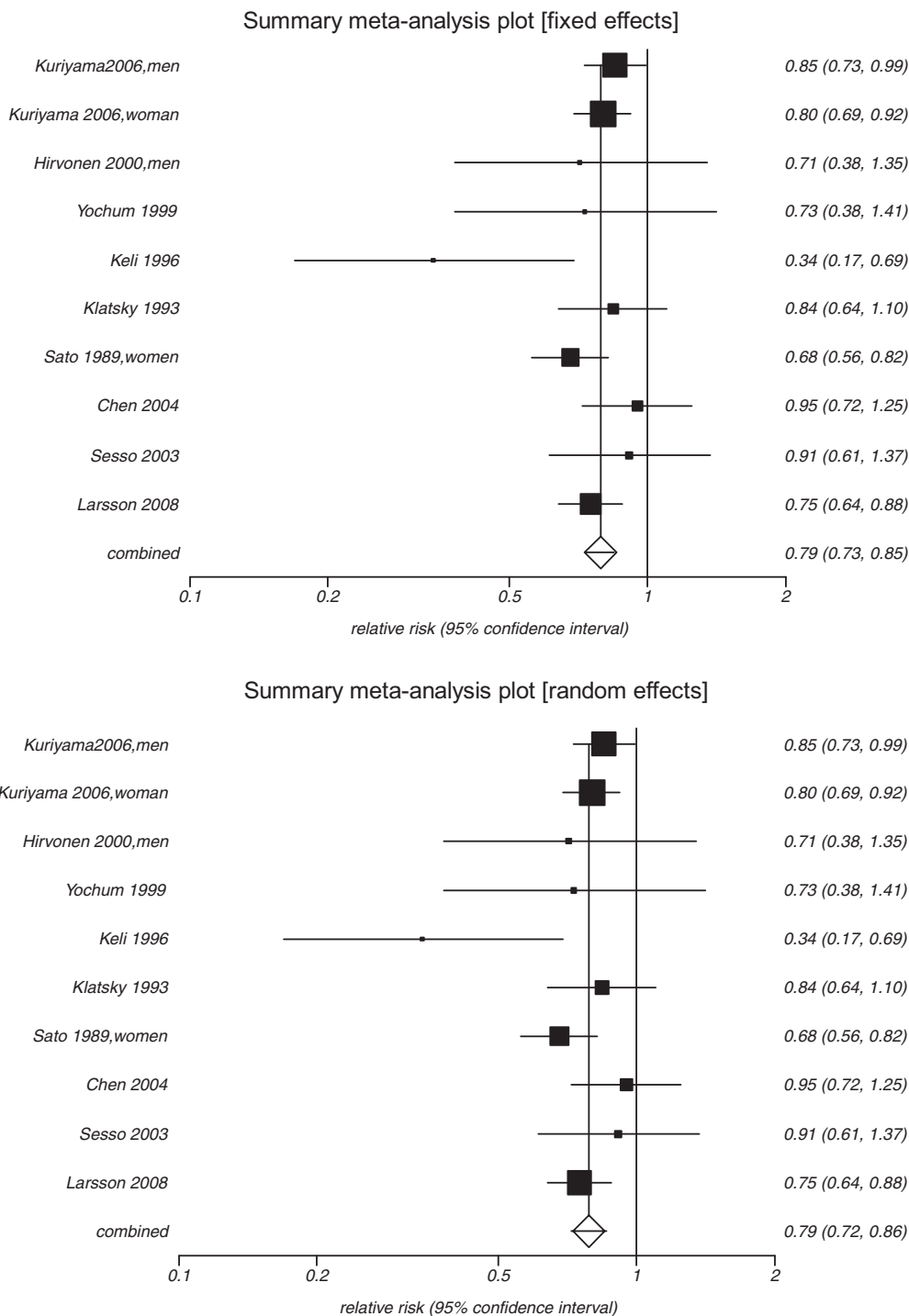


Figure 2. Forest plot of studies of stroke and tea consumption.

831 stroke events were hemorrhagic. The third study was in a Japanese population³⁴ in which only 34 of the 145 stroke deaths were reported to be hemorrhagic. In each case, the risk ratios for hemorrhagic stroke were close to 1.0. Thus, the overriding association is likely to be due primarily to the effect of tea on ischemic stroke. Ischemic stroke is 10 times more frequent than intracerebral hemorrhage and 30 times more frequent than subarachnoid hemorrhage among 85 year olds in the United States.³⁵ Although hemorrhagic stroke has traditionally been more

frequently experienced in Asia, ischemic stroke is also a major problem there as evidenced by the low number of hemorrhagic strokes in Japan.

The mechanism of action by which tea may protect against stroke remains speculative. Although antioxidant functions and anti-inflammatory actions are often mentioned, 3 mechanisms have some in vivo evidence of effect or lack of it. One is the relationship between black and green tea and blood pressure. Both types of tea have been shown to reduce blood pressure in stroke-prone hypertensive rats at doses equivalent

Table 2. Meta-Analysis Results Relative Risk per 3 Cups of Tea

	No. of Studies	Fixed-Effects Model		Random-Effects Model		Tests of Homogeneity				Test of Publication Bias	
		RR	95% CI	RR	95% CI	Q Value	df	P	I ²	Begg P	Egger P
Stroke	10	0.79	0.73–0.85	0.79	0.72–0.86	11.8	9	0.224	23.8%	0.38	0.44
Cohort	9	0.78	0.72–0.84	0.77	0.71–0.85	9.9	8	0.27	19.4%	0.26	0.30
Black tea	6	0.76	0.67–0.86	0.76	0.64–0.89	6.4	5	0.266	22.3%	0.47	0.48
Green tea	3	0.79	0.72–0.86	0.78	0.69–0.88	3.29	2	0.193	39.2%	—	—
Asian	4	0.80	0.74–0.88	0.80	0.72–0.90	4.89	3	0.180	38.6%	0.75	0.80
Non-Asian	6	0.76	0.67–0.86	0.76	0.64–0.89	6.64	5	0.266	22.3%	0.47	0.48

to 1 L per day in humans.³⁶ Blood pressure control is the primary strategy to limit risk of stroke in humans. However, population-based analyses do not support a generalized negative association between tea consumption and blood pressure.³⁷

A second mechanism is through an impact of tea or catechin consumption on nitric oxide formation.³⁸ Catechin ingestion blocked an increase in serum nitric oxide concentration in rats after reperfusion and tea has a demonstrated effect on endothelial function. Ingested tea can also enhance endothelial function, especially among those with compromised functionality.^{32,39} Because cerebral blood flow is particularly impaired in elderly with reduced endothelial function, and vascularization of the brain impacts stroke risk, this is a possible mechanism.⁴⁰

The third possibility is through effects of theanine, an amino acid in high concentrations in and coming almost exclusively from the tea plant. Theanine is readily bioavailable from both green and black tea, crosses the blood–brain barrier, and has demonstrated effects on brain function.⁴¹ The chemical structure of theanine, which contains the glutamate molecule, suggests that it might reduce glutamate-related endothelial damage. Studies of middle cerebral artery occlusion in mice have demonstrated a neuroprotective effect of γ -glutamylethylamide (theanine) and at dosages of 0.5 and 1.0 mg/kg, it reduces the size of the cerebral infarct in the gerbil. In this model, functional γ -aminobutyric acid_A receptors, present only in the brain, appear to be responsive to theanine.⁴²

An alternative hypothesis, supported by the experiments with induced focal ischemia, is that regular tea consumption, instead of preventing overt stroke, may instead reduce the postischemic damage to a level that results in subclinical ischemia or hidden strokes. This would result in the diagnosis of stroke only in individuals with more extensive postischemic damage or a greater stroke volume.

In conclusion, the observational epidemiological research in humans is strongly supportive of the hypothesis that tea consumption, at the level of ≥ 3 cups per day, either as green or black tea, reduces the risk of occurrence of stroke, stroke volume, and mortality from stroke.

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