Tea consumption and cardiovascular disease risk[1–3]

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ABSTRACT

Background: The present analysis was conducted in response to inconsistent epidemiologic studies on the relation between consumption of tea and cardiovascular diseases.

Objective: We undertook a literature review of the consistency and strength of the associations between tea and cardiovascular diseases on the basis of published observational studies and meta-analyses addressing tea or tea flavonoids and cardiovascular disease risk.

Design: We performed a search in 3 databases for meta-analyses and compared them with studies they subsumed. We performed an additional search for subsequent studies to determine whether the conclusions were consistent.

Results: Many epidemiologic studies have been conducted and summarized in 5 meta-analyses on either tea consumption or flavonoid consumption and cardiovascular disease or the subset of stroke. Heterogeneity of effect was seen when the outcome included all cardiovascular diseases. In the case of stroke, a consistent, dose-response association with tea consumption on both incidence and mortality was noted with RRs of 0.80 (95% CI: 0.65, 0.98) for flavonoids and 0.79 (95% CI: 0.73, 0.85) for tea when high and low intakes were compared or the addition of 3 cups/d was estimated.

Conclusion: Thus, the strength of this evidence supports the hypothesis that tea consumption might lower the risk of stroke.

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INTRODUCTION

Due to the frequent and widespread consumption of tea and coffee and the physiologic effects of caffeine on heart rate and blood pressure (1), concern about the cardiovascular impact of heavy consumption has been raised. Although early reports related coffee consumption to increased cardiovascular disease risk (2–5), over time concerns have dissipated; and more recently, coffee consumption has been associated with decreased risk of type 2 diabetes, which is one of the strongest risk factors for cardiovascular disease (6). In contrast, although much attention has been given to the large family of flavonoids of which tea is a major dietary source, a consensus regarding an association between tea and cardiovascular disease has not been reached. Some observational epidemiologic studies have suggested that tea consumption might play a role in lowering cardiovascular disease. A number of plausible mechanisms have been identified for this relation, but the information across studies, countries, and types of tea and disease outcomes do not appear to be consistent. This is a review of the large body of epidemiologic evidence of a relation between tea and cardiovascular disease.

METHODS

The selection of studies and extraction of data from articles was independently conducted by 2 authors (FK and LA). The initial intent was to conduct a systematic literature review of all original epidemiologic research on tea consumption and cardiovascular disease. However, because this search yielded 570 studies and a number of meta-analyses that summarized the data, we chose to *1*) search for meta-analyses on the subject, *2*) compare them with the studies they subsumed, and *3*) determine whether studies subsequent to the most recent meta-analysis contradict earlier conclusions. The search for meta-analyses was conducted to identify original epidemiologic research examining the association between tea consumption and cardiovascular disease. Potential eligible studies were identified through an electronic search of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) conducted in October 2012. The search used the following terms to identify the risk exposure (tea or flavonols or flavonoids) combined with terms to determine the outcomes of interest (heart disease or cardiovascular disease or stroke or coronary). The searches were performed to include the key word meta-analysis with the above terms. There were no language restrictions on the search. We screened titles, key words, and abstracts of the citations obtained from the database. If deemed appropriate for our study, a full copy of the article was obtained for further assessment. We included meta-analyses that addressed the relation between tea or flavonol consumption and heart disease. Articles that were cross-sectional or that did not study humans were excluded. Articles in which tea or flavonols were not studied were excluded. Articles in which heart disease or stroke incidence was not measured were excluded as well. Extending the search by using the same criteria in Web

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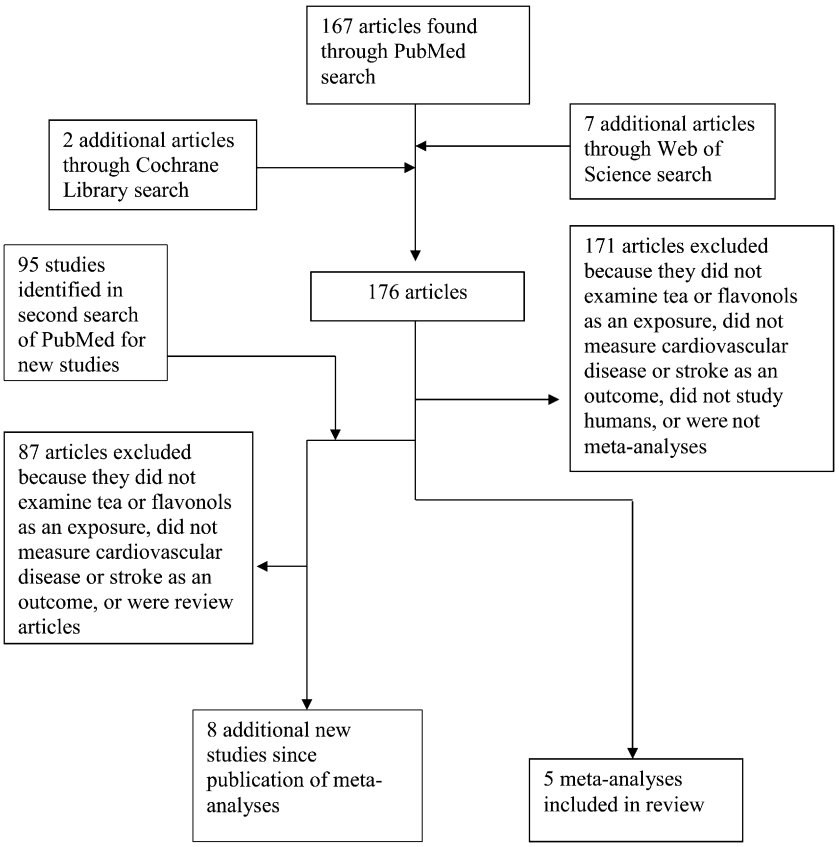

FIGURE 1. Search outcomes. (Cochrane Library: http://www.thecochranelibrary.com/view/0/index.html; PubMed: http://www.ncbi.nlm.nih.gov/pubmed; Web of Science: http://apps.webofknowledge.com/UA_GeneralSearch_input.do?product=UA&search_mode=GeneralSearch&SID=2CyPaVg9lSPJY3QWmH1&preferencesSaved=).

of Science (http://apps.webofknowledge.com/UA_GeneralSearch_input.do?product=UA&search_mode=GeneralSearch&SID=2CyPaVg9lSPJY3QWmH1&preferencesSaved=) yielded an additional 7 studies, whereas further searches in the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html) yielded an additional 2 articles. The Supplemental Appendix under "Supplemental data" in the online issue shows the search strategy. The outcome of the search for the meta-analyses is shown in **Figure 1**.

Another search was performed to identify studies subsequent to the most recent meta-analyses through the PubMed database. The search used the same search criteria as mentioned above; however, only studies published after 2009 were deemed eligible for further examination. The strategy for this search is shown in the Supplemental Appendix under "Supplemental data" in the online issue, and the results of the search are shown in Figure 1.

RESULTS

Most of the studies with the key words mentioned previously were not meta-analyses of the outcome of interest in relation to tea consumption. Only 5 meta-analyses met the inclusion criteria for measuring the effects of tea or flavonols on cardiovascular disease. The meta-analyses were published between 2001 and 2011 (7–11). Their risk estimates are summarized in **Table 1**, and details on the studies are included in **Table 2**. The RR estimates of each study are shown in **Figure 2**. Each meta-analysis included a different subset of studies. The overlap in studies included in these 5 meta-analyses is presented in **Table 3** (4, 5, 12–44).

The meta-analysis by Wang et al (11) included 6 case-control and 12 cohort studies. Of these 18 studies, 13 measured black tea as the exposure, whereas the other 5 used green tea as the exposure studied. The outcomes considered were myocardial infarction (MI)[4], coronary heart disease (CHD) incidence and mortality, ischemic heart disease, and coronary artery disease (CAD). For black tea, 6 of the 13 studies were conducted in the United States, 2 in the United Kingdom, and 5 in continental Europe; and there was significant heterogeneity between the studies (P = 0.039, I^2 = 42.9%). All 5 studies on green tea were in Asian populations, 3 from Japan and 2 from China. There was no significant heterogeneity between the study results (P = 0.314, I^2 = 15.5%). The meta-analysis concluded that no significant protective role for black tea was shown, but for green tea, the summary RR indicated a reduced risk of CAD by 28% (RR: 0.72; 95% CI: 0.58, 0.89) and an associated 10% decrease in risk with an increase in consumption of green tea by 1 cup/d (RR: 0.90; 95% CI: 0.82, 0.99). The meta-analysis conducted by Peters et al (7) included 10 cohort studies and 7 case-control studies. Seven studies were from the United States, 2 from the United Kingdom, 5 from continental Europe, 1 from Japan, and 1 from Australia. The meta-analysis focused primarily on the association between tea intake and rates of cardiovascular disease. which included stroke, MI, and all incidences of CHD. In

[4]Abbreviations used: CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction.

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TABLE 1
Risk estimates from meta-analyses of tea or flavonoids and cardiovascular disease[1]

First author (reference)	Year	RR (95% CI)	Exposure	Contrast	Outcome	*P* value (I^2)	Publication bias	Dose response
Peters (7)	2001	0.89 (0.79, 1.01)	Tea	3 cups tea/d vs 0 cups/d	MI	0.20	Begg and Mazumdar test, funnel suggested bias	Not addressed
Arab (8)	2009	0.79 (0.73, 0.85)	Tea	3 cups tea/d vs 0 cups/d	Stroke	0.22 (24%)	Funnel graph, Egger's regression, Begg found no bias	Not addressed
Hollman (9)	2010	0.80 (0.65, 0.98)	Flavonoid	Top third vs bottom third for flavanol intake	Stroke	0.05 (54%)	Begg, funnel plot Egger's test found bias ($P = 0.01$)	Not addressed
Huxley (10)	2003	0.80 (0.69, 0.93)	Flavonol	Top third vs bottom third for flavanol intake	CHD mortality	<0.001	Not addressed	Not addressed
Wang (11)	2011	0.92 (0.82, 1.04)	Black tea	Increase of 1 cup black tea/d	CAD	0.039 (43%)	Egger's regression asymmetry test ($P = 0.380$)	No dose-response (RR: 0.98; 95% CI: 0.94, 1.02; $P = 0.000$, $I^2 = 74.8\%$)
Wang (11)	2011	0.72 (0.58, 0.89)	Green tea	Increase of 1 cup green tea/d	CAD	0.314 (15%)	Egger's regression asymmetry test ($P = 0.380$)	10% decrease per cup/d (RR: 0.90; 95% CI: 0.82, 0.99; $P = 0.000$, $I^2 = 86\%$)

[1] CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction.

this study, a meta-regression was conducted to estimate the difference in risk per additional consumption of 3 cups tea/d. Most of the studies included suggested a decrease in the rate of cardiovascular disease incidence with increasing tea consumption. However, at that time, the evidence was limited to a few studies, and the summary estimates for stroke and CAD were too heterogeneous to be summarized ($P < 0.02$ for stroke, $P < 0.001$ for CAD). The incidence rate of MI decreased by 11% with an increase in tea consumption of 3 cups/d (RR: 0.89; 95% CI: 0.79, 1.01; $P = 0.20$). Regional differences may have contributed to the heterogeneity of effect.

Although conducted 10 y apart, both of these meta-analyses of tea consumption and cardiovascular disease, one of which considered 18 studies (11), the other 17 studies (7) with 5 studies differing between them, reported similar estimates of RR per cup of tea. In the Peters et al (7) study, because of the heterogeneity of effect across studies, the risk estimate could only be summarized across the United States and Europe for MI as 0.89 (95% CI: 0.79, 1.01), where most of the consumption was of black tea. In the Wang et al (11) analysis, the risk estimate for CAD was estimated to be nonsignificant at 0.92 (95% CI: 0.82, 1.04) for black tea and 0.72 (95% CI: 0.58, 0.89) for green tea. Both studies reported heterogeneity of effect for the cardiovascular outcomes they summarized (Table 2).

Two of the meta-analyses considered all flavonoids, not just tea. The meta-analysis by Huxley and Neil (10) included 7 prospective cohort studies that explored the association between flavonoids and CHD. Dietary intake of flavonols was assessed from food-frequency questionnaires or interviews with a trained dietitian. The range of intake of flavonols ranged from 2 to 34 mg/d. In the populations with the highest reported flavonol intakes, tea was the primary source of flavonols; in the lowest bracket, fruit and vegetables were the principal sources. There was evidence of significant heterogeneity between the studies ($P < 0.001$). They reported a 20% reduction in cardiovascular disease among individuals exposed to higher amounts of flavonols, with a risk estimate of 0.80 (95% CI: 0.69, 0.93). The meta-analysis by Hollman et al (9) included 6 cohort studies that measured the association of flavonol intake with fatal and nonfatal stroke. Exposure to flavonols was estimated by using food-frequency questionnaires and assessing dietary intake at baseline. Tea was most likely the major contributor of flavonols in all the cohorts, although its contribution varied between the countries. Onions and apples were the other major sources of flavonols. The 6 cohorts were from 3 countries: The Netherlands, Finland, and the United States. Stroke endpoints in these studies were either not specified or not analyzed separately and combined with ischemic and hemorrhagic stroke. Heterogeneity was moderate ($P = 0.05$, $I^2 = 54\%$). The authors reported a risk estimate of 0.80 (95% CI: 0.65, 0.98), consistent with the meta-analysis of Arab et al (8), which combined 11 studies on stroke and tea consumption and calculated the RR reduction per cup of tea to be 21%, on average, with a RR of 0.79 (95% CI: 0.73, 0.85). All of the studies included in Arab et al (8) had risk point estimates <1.0, with CIs all <1.0, with no significant heterogeneity. A consistent association was found with tea consumption and reduced risk for occurrence of and mortality from stroke. This association did not appear to be specific to green or black tea or to Asian or non-Asian populations.

The search for new studies showed an additional 8 studies of tea and stroke risk published since the meta-analyses were conducted

TABLE 2
Details of meta-analyses of tea or flavonol exposure on cardiovascular disease risk[1]

	First author (reference)				
	Peters 2001 (7)	Arab 2009 (8)	Hollman 2010 (9)	Huxley 2003 (10)	Wang 2011 (11)
Study type and number	17 studies: 10 cohort studies and 7 case-control studies	11 studies: 8 cohort studies, 2 case-control studies, and 1 cross-sectional study	6 cohort studies	7 cohort studies	18 studies: 12 cohort studies and 6 case-control studies
Years of study	1980–1991	1989–2008	1996–2009	1966–2001	1966–2009
Exposure studied	Did not distinguish between black or green tea; tea intake calculated as cups/d	6 studies on black tea, 3 studies on green tea; tea exposure calculated as cups/d	Flavonol intake calculated the sum of quercetin, kaempferol, and myricetin; flavones calculated the sum of luteolin and apigenin in mg/d	Flavonol intake calculated from dietary intake of tea, apples, onions, broccoli, or vegetables in mg/d	13 studies on black tea, 5 studies on green tea; tea exposure calculated as cups/d
Outcomes considered	MI, stroke, and/or CHD incidence rate	Nonfatal and fatal stroke incidence rate	Nonfatal and fatal stroke incidence rate	CHD mortality	CAD risk incidence, MI, CHD, IHD, coronary death
All exposures	CHD: too heterogeneous to combine all studies; RR calculated for the addition of 3 cups/d Continental Europe (3 studies) (RR: 0.27; 95% CI: 0.14, 0.50; $P = 0.95$) USA (8 studies) (RR: 0.95; 95% CI: 0.84, 1.08; $P = 0.30$) MI (7 studies) (RR: 0.89; 95% CI: 0.79, 1.01; $P = 0.20$)	RR calculated for the addition of 3 cups/d ($n = 10$) (RR: 0.79; 95% CI: 0.73, 0.85; Q value = 11.8, $df = 9$, $P = 0.224$, $I^2 = 23.8\%$)	High intake of flavonols of 16–47 mg/d (RR: 0.80 (95% CI: 0.65, 0.98) vs low intake (4–14 mg/d) ($P = 0.05$; $I^2 = 54\%$)	Highest third of flavonol intake (RR: 0.80; 95% CI: 0.69, 0.93) vs lowest ($\chi^2 = 38.60$, $df = 6$, $P < 0.001$)	—
Black tea	—	$n = 6$ (RR: 0.76; 95% CI: 0.67, 0.86; Q value = 6.4, $df = 5$, $P = 0.266$, $I^2 = 22.3\%$)	—	—	High vs low (RR: 0.92; 95% CI: 0.82, 1.04; $P = 0.039$, $I^2 = 42.9\%$); per cup/d (RR: 0.98; 95% CI: 0.94, 1.02; $P = 0.000$; $I^2 = 74.8\%$)
Green tea	—	$n = 3$ (RR: 0.79; 95% CI: 0.72, 0.86; Q value = 3.29, $df = 2$, $P = 0.193$, $I^2 = 39.2\%$)	—	—	High vs low (RR: 0.72; 95% CI: 0.58, 0.89; $P = 0.314$, $I^2 = 15.5\%$); per additional cup/d (RR: 0.90; 95% CI: 0.82, 0.99; $P = 0.000$, $I^2 = 86.1\%$)

[1] CAD, coronary artery disease; CHD, coronary heart disease; IHD, ischemic heart disease; MI, myocardial infarction; *P*, *P* value for heterogeneity; —, data not provided.

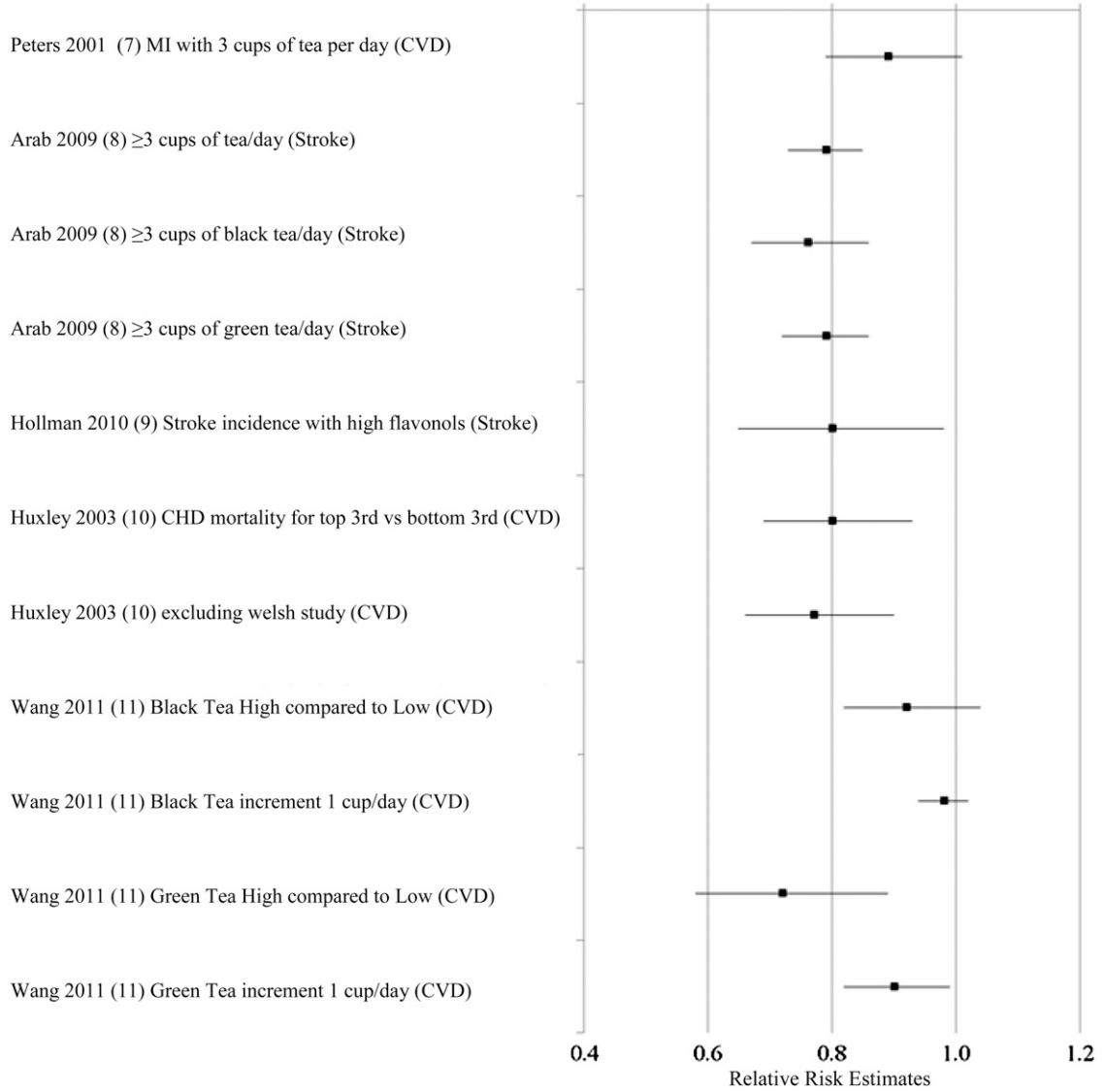

FIGURE 2. Tree plot of RR estimates and ORs for tea and cardiovascular disease by type of tea. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

(45–52). The details of these studies are presented in **Table 4**; the RRs for these studies are represented in **Figure 3**, where it can be seen that the point estimates for risk were consistently below 1.0, except for the consumption of oolong tea, which was less frequent than once a day (where the risk estimate was equal to 1.0).

DISCUSSION

The term "cardiovascular disease" encompasses a wide range of diverse disease entities that differ in their etiology and pathology (53). This level of specificity is lacking in the epidemiologic studies, which, with the exception of the studies on stroke, combine many of these disease entities, rely on disease coding that is uneven, and, for the sake of simplicity and greater numbers, often include morbidity and mortality in the same risk analyses. In general, the broadly categorized cardiovascular disease studies show heterogeneity of results. In contrast, both of the meta-analyses of stroke outcomes, which summarize data from 14 studies, show almost identical risk estimates (0.79 and 0.80) and narrow CIs, which differs significantly from the null hypothesis. These epidemiologic findings support a potential protective role and, with great certainty, no detrimental influence of tea consumption on stroke risk. These findings also provide weaker support for other cardiovascular disease entities.

An understanding of possible mechanisms of effects is provided by animal studies in which both black and green tea have been shown to reduce blood pressure in stroke-prone hypertensive rats at doses equivalent to 1 L/d in humans (54). In addition, both tea and catechin consumption in animal studies showed that catechin ingestion blocked increases in serum nitric oxide concentration in rats after reperfusion (55). Another possible mechanism shown in humans is the proven effect of tea consumption on improving impaired endothelial function, a correlate of blood pressure (56, 57).

The strengths of this analysis include the large number of peer-reviewed studies that are published on this topic and the consistency of findings. In addition, although it would be desirable to have precise measurements of the gram amount of tea leaves

TABLE 3
Original publications included in the meta-analyses[1]

First author of meta-analysis and year (reference)	First author (reference)				
	Wang (11)	Hollman (9)	Huxley (10)	Peters (7)	Arab (8)
BCDSP 1972 (4)	—	—	—	Yes	—
Chen 2004 (12)	—	—	—	—	Yes
Geleijnse 2002 (13)	Yes	—	—	—	—
Gramenzi 1990 (14)	—	—	—	Yes	—
Hertog 1993 (15)	Yes	—	Yes	Yes	—
Hertog 1994 (16)	Yes	—	—	—	—
Hertog 1997 (17)	—	—	Yes	Yes	—
Hirano 2002 (18)	Yes	—	—	—	—
Hirvonen 2000 (19)	—	Yes	—	Yes	Yes
Hirvonen 2001 (20)	Yes	—	Yes	—	—
Jick 1973 (5)	—	—	—	Yes	—
Keli 1996 (21)	—	Yes	—	Yes	Yes
Klatsky 1993 (22)	Yes	—	—	Yes	Yes
Knekt 2002 (23)	—	Yes	Yes	—	—
Kuriyama 2006 (24)	Yes	—	—	—	Yes
Larsson 2008 (25)	—	—	—	—	Yes
Lopez-Garcia 2006 (26)	Yes	—	—	—	—
Mink 2007 (27)	—	Yes	—	—	—
Mursu 2008 (28)	—	Yes	—	—	—
Nakachi 2000 (29)	Yes	—	—	—	—
Okamoto 2006 (30)	—	—	—	—	Yes
Rimm 1996 (31)	—	—	Yes	Yes	—
Rosenberg 1980 (32)	—	—	—	Yes	—
Rosenberg 1988 (33)	—	—	—	Yes	—
Rosenberg 1998 (34)	Yes	—	—	—	—
Sato 1989 (35)	—	—	—	Yes	Yes
Sesso 1999 (36)	Yes	—	—	Yes	—
Sesso 2003 (37)	Yes	Yes	—	—	Yes
Stensvold 1992 (38)	Yes	—	—	Yes	—
Tavani 2001 (39)	Yes	—	—	—	—
Thrift 1996 (40)	—	—	—	Yes	Yes
Wang 2010 (41)	Yes	—	—	—	—
Wen 2008 (42)	Yes	—	—	—	—
Woodward 1999 (43)	Yes	—	—	Yes	—
Yochum 1999 (44)	Yes	—	Yes	Yes	Yes

[1] BCDSP, Boston Collaborative Drug Surveillance Program; —, article not included in meta-analysis.

used, the measurement of tea consumption is reasonably good for a dietary component. Unlike other beverages, such as sodas or alcoholic beverages, reporting is unlikely to be biased by social desirability. Furthermore, the outcomes in the cardiovascular area are subject to coding biases, and strokes tend to be underreported but are not likely to be reported in the absence of the condition. Thus, exposure and outcomes are reasonably strongly assessed. Another strength is the diversity of the populations and consumption patterns, which adds robustness to the findings. Most significantly, as seen in both Figures 2 and 3, the point estimates and CIs are consistently preventive among the studies included in the meta-analyses and those published subsequently, regardless of study population or specific outcome.

Nonetheless, the analysis has limitations. Chief among these, the assessment of beverage consumption is largely at a single point in time, mostly at baseline, and changes in intakes over time are not accounted for in the risk assessments. Also, the questionnaires were semiquantitative and largely categorical in their assessment of tea consumption. Because tea and coffee consumption are generally inversely related, studies need to control for coffee to ensure that the tea effect is not a "non–coffee effect." Also, despite the fact that each of the primary studies calculated their risk estimates after adjusting for covariates such as age, education, sex, smoking, family history, and cardiovascular risk, residual confounding is a limitation here, as with all observational studies. Last, another limitation is that the question of whether green or black tea is more potent cannot be answered because there is not enough diversity of intake of both of these within Asian and non-Asian populations.

CONCLUSIONS

In conclusion, considerable observational human evidence suggests a preventive association of tea or flavonoid intake on specific subcategories of cardiovascular disease. Studies that use less specific outcomes are less likely to show a significant association. When the outcome is restricted to stroke incidence or mortality, the association seems to be the strongest and most consistent. The strength and consistency of the relation, along with the supportive data in preclinical studies using animal

TABLE 4
Details of additional studies of tea exposure on CVD risk[1]

	First author (reference)							
	Ko (45)	Mostofsky (46)	de Koning Gans (47)	Leurs (48)	Mineharu (49)	Liang (50)	Pyshchyta (51)	Kokubo (52)
Study type, number of participants	Case-control, 233	Multicenter case-crossover, 390	Cohort, 37,514	Cohort, 120,852	Cohort, 76,979	Case-control, 374	Cohort, 1340	Cohort, 82,369
Years of study	2011	2001–2006	2010	1986–1996	2011	2007–2008	2003–2011	1995–2007
Exposure studied	Green tea	Caffeine from tea	Tea	Tea	Green, black, and oolong teas	Tea	Tea	Green tea
Outcomes considered	Lacunar infarction incidence	Ischemic stroke incidence	Stroke and coronary heart disease morbidity and mortality	Ischemic heart disease or stroke mortality	CVD mortality	Ischemic stroke incidence	Acute myocardial infarction incidence	Stroke incidence
RR estimate (95% CI)	>1 cup vs 0 cups tea/d: 0.30 (0.16, 1.77)	Tea consumption immediately before stroke: 0.90 (0.40, 2.00)	>6 cups vs 0 cups tea/d: 0.64 (0.46, 0.90)	>1 cup vs 0 cups tea/d: 0.91 (0.83, 1.00)	>6 cups vs 0 cups green tea/d: 0.42 (0.17, 0.88); >6 cups vs 0 cups oolong tea/d: 0.39 (0.17, 0.88); no association for black tea (P = 0.467)	Tea intake of >1 cup vs 0 cups/d: 0.61 (0.40, 0.94); duration of drinking >20 vs ≤20 y: 0.40 (0.25, 0.64); average tea leaves brewed >3 vs 0 kg/y: 0.27 (0.16, 0.46)	>1 cup vs 0 cups tea/d: 0.78 (0.64, 0.95)	≥4 cups vs 0 cups green tea/d: 0.80 (0.73, 0.89)

[1] CVD, cardiovascular disease.

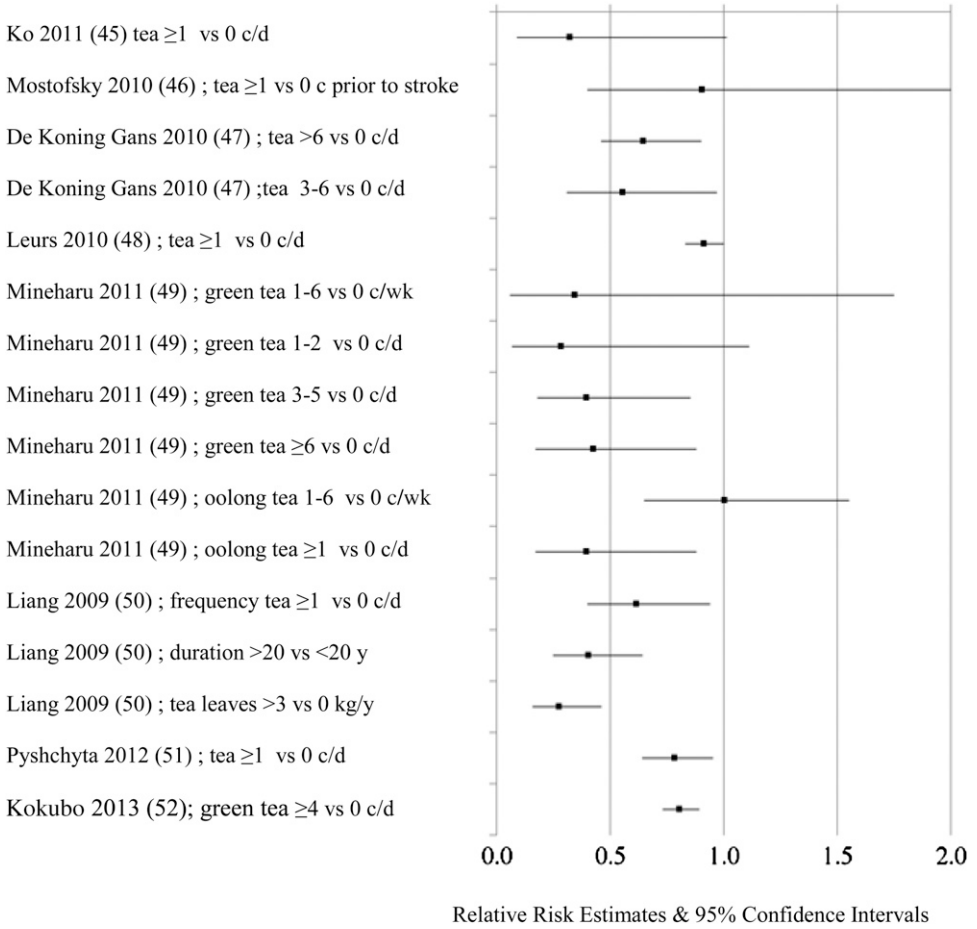

FIGURE 3. Tree plot of RR estimates and ORs for tea and cardiovascular disease from studies not included in meta-analyses. c, cup.

models, lend credence to a correlation between tea and stroke under modern living conditions regardless of geography and ethnicity.

Although the evidence appears to be stronger for green tea than for black tea, which differ greatly in their flavonoid profiles, it is difficult to compare this evidence because the populations and their baseline risks of cardiovascular disease differ greatly between the individual studies on these 2 types of tea, and few studies of green tea provide evidence in non-Asian populations.

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